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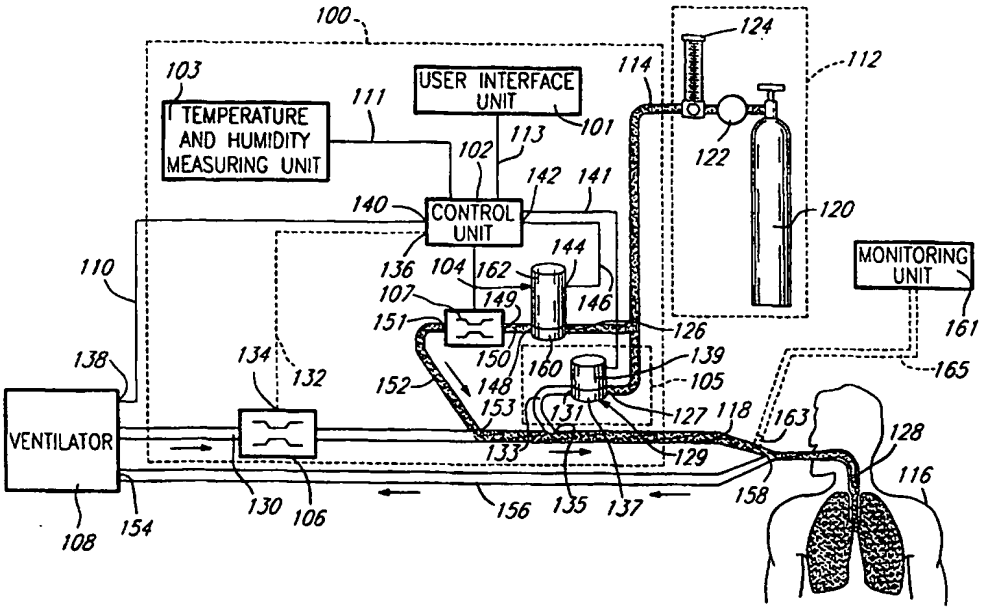


(57) Abstract

An injection system (100) for the delivery of a gaseous substance (112) to a patient respiratory system is described herein. The injection system (100) includes a control unit (102) and a valve assembly (104) including a valve (160) and a valve actuator (162) allowing partial opening of the valve (160) and controlled by the control unit (102). The control unit (102) is supplied with gas flow data and controls the valve assembly (104) so that the opening of the valve (160) is a function to the gas flow to thereby enable the control over the concentration of the gaseous substance (112) delivered to the patient (116).

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## TITLE OF THE INVENTION

INJECTION SYSTEM FOR DELIVERY OF A GASEOUS SUBSTANCE

## FIELD OF THE INVENTION

The present invention relates to an injection system for delivery of a gaseous substance. More specifically, the present invention relates to an injection system for delivery of a gaseous substance to a patient, where the concentration of the gaseous substance delivered to the patient may be modified during the patient inspiratory phase and may be gradually modified over a predetermined number of patient inspiratory phases.

## BACKGROUND OF THE INVENTION

It has been found that various chemical compounds, such as, for example, nitric oxide (NO), administered during a patient inspiratory phase may provide beneficial effects.

For example, NO presents some lung vasodilator properties that may be helpful for respiratory distress conditions such as respiratory distress syndrome of newborn.

Apparatus for delivering such gaseous chemical compounds have therefore been designed to deliver the compounds during the patient's inspiratory phase.

One such apparatus is described in Canadian Patent Application N° 2,106,696, filed on September 22, 1993 and published on March 25, 1994 and naming Robert Briand and Marie-Hélène Renaudin as inventors. In this document, Briand et al. describe an apparatus for delivering controlled doses of NO to the respiratory system of the patient without conventional pre-mixing of the NO with oxygen supplied by a ventilator device. The apparatus therefore includes means for detecting the beginning of a patient inspiratory phase and to open an electromagnetic valve for a predetermined duration to supply a controlled dose of NO. The duration and the pressure of the NO supplied dose is adjusted so as to obtain the desired NO concentration with respect to the average inhalation volume of the patient. The NO dose supplied is therefore not directly related to the inhalation volume of the patient. Of course, there is no NO injection during the expiration phase.

A major drawback of the apparatus described by Briand et al. is the automatic opening of the electromagnetic valve for a predetermined duration each time the beginning of an inhalation phase is detected. Indeed, if the patient repetitively draws short breaths, harm may be caused by the high concentration of NO injected to the patient.

In an article entitled: "Comparison of two administration techniques on inhaled nitric oxide on nitrogen dioxide production", published in Canadian journal of Anaesthesiology 1995, Vol. 42:10, pages 922-927, Dubé et al. describe an injection system for delivering NO during inspiratory phase. In this injection system, an electronic circuit detects the beginning and the end of each inspiration by processing a flow signal supplied by a ventilator. At the beginning of the inspiratory

phase, the electronic circuit opens a solenoid valve and NO is injected into the respiratory line. At the end of the inspiratory phase, the electronic circuit closes the solenoid valve and the injection of NO is stopped.

Figure 1 of the appended drawings is a graph of the inspiratory gas flow 20 vs time for a conventional ventilator when the ventilator is in a first mode. When it is in this mode, the flow of inspiratory gas is constantly delivered for a predetermined duration (inspiratory phase 22) and the patient then expires (expiratory phase 24). In the injection system proposed by Dubé et al., when the gas flow reaches a predetermined threshold level 26, a solenoid valve is open, delivering NO to the patient. The line 28 illustrates the injected flow of NO in the inspiration circuit over time. It is to be noted that the scale is different for the flow of inspiratory gas 20 and the flow 28 of NO. Indeed, line 28 illustrating the flow of NO is shown scaled up for illustrative purposes.

Since the solenoid valve used by Dubé et al. is of the type fully open/fully closed, the flow 28 of NO is constant when the valve is open. As can be seen from Figure 2, the concentration 29 of NO is essentially constant over time during the inspiratory phases. When the inspiratory gas flow 20 falls below the threshold level 26, the solenoid valve is closed, stopping the flow of NO.

Figure 3 is a graph of the inspiratory gas flow 30 vs time for a conventional ventilator when the ventilator is in a second ventilating mode. When it is in this mode, the flow of gas is not constantly delivered

for a predetermined duration but follows a particular curve during the inspiratory phase 32 and the patient then expires (expiratory phase 34). In the injection system proposed by Dubé et al., when the gas flow reaches a predetermined threshold level 36, the solenoid valve is open delivering NO to the patient. The line 38 illustrates the flow of NO over time. Again, it is to be noted that the scale is different for the flow of inspiratory gas and the flow 38 of NO. Indeed, line 38 illustrating the flow of NO is shown scaled up for illustrative purposes.

Since the solenoid valve used by Dubé et al. is of the type fully open/fully closed, the flow of NO is constant when the valve is open. As can be seen from Figure 4, the concentration of NO (line 39) is not constant over time during the inspiratory phases but varies inversely with the flow of gas since the flow of NO is constant. When the inspiratory gas flow 30 falls below the threshold level 36, the solenoid valve is closed.

A drawback of the injection system of Dubé et al. is that, in certain cases, the NO concentration is not constant during the inspiratory phase.

Canadian patent application N° 2,133,516 filed on October 3rd, 1994 and naming Bathe *et al.* as inventors describes a nitric oxide (NO) delivery system monitoring the inspiratory gas flow of a patient and controlling a proportional valve to allow a calculated flow of NO to enter the inspiratory gas flow. The delivery system calculates the flow of NO in order to maintain a constant, user programmable, NO concentration in the inspiratory gas.

A drawback of the delivery system of Bathe *et al.* is that, while the delivery system may be programmed so that the concentration of NO in the inspiratory gas flow is constant, there are no provisions to modify the concentration of the NO during a particular inspiratory phase, or to program the variation of the concentration of NO over a number of successive inspiratory phases in view of gradually increasing or decreasing the concentration of NO supplied to the patient.

## OBJECTS OF THE INVENTION

An object of the present invention is therefore to provide an improved apparatus for the delivery of gaseous substances.

## SUMMARY OF THE INVENTION

More specifically, in accordance with the present invention, there is provided an injection system for the delivery of a gaseous substance from a container to a patient through a conduit coupled to the patient respiratory system; the injection system comprising:

a control unit controlling the injection system;

a valve assembly in connection with the conduit to selectively allow the delivery of the gaseous substance from the container to the conduit; the valve assembly including a valve and valve actuating means allowing variable opening of the valve; the valve actuating means being coupled to the control unit to be controlled thereby;

a flowmeter quantitatively measuring inspiratory gas flow in the conduit; the flowmeter being coupled to the control unit to supply inspiratory gas flow data thereto;

the control unit controlling the valve assembly so that the variable opening of the valve is responsive to the inspiratory gas flow in the conduit.

According to another aspect of the present invention, there is provided an injection system for the delivery of a gaseous substance from a container to a patient through a conduit coupled to the patient respiratory system; the respiratory system of the patient being also coupled to a ventilator forcing inspiratory gas therein; the injection system comprising:

a control unit controlling the injection system; the control unit receiving inspiratory gas flow data from the ventilator;

a valve assembly in connection with the conduit to selectively allow the delivery of the gaseous substance from the container to the conduit; the valve assembly including a valve and valve actuating means allowing variable opening of the valve; the valve actuating means being coupled to the control unit to be controlled thereby;

the control unit controlling the valve assembly so that the variable opening of the valve is responsive to the inspiratory gas flow supplied to the patient.

A major advantage of the present invention concerns the variable opening of the valve to increase or decrease the quantity of the gaseous substance delivered to the patient. Hence, it is possible to control the opening of the valve so that the variable opening of the valve

is responsive to the inspiratory gas flow directed towards the respiratory system of the patient and thereby controlling the concentration of the gaseous substance delivered to the patient.

Other objects, advantages and features of the present invention will become more apparent upon reading of the following non restrictive description of preferred embodiments thereof, given by way of example only with reference to the accompanying drawings.

The subject of the present invention was developed at *"Le Département de physique biomédicale, Pavillon Notre-Dame, Centre hospitalier de l'Université de Montréal (CHUM)"*

## BRIEF DESCRIPTION OF THE DRAWINGS

In the appended drawings:

Figure 1, which is labelled "PRIOR ART", illustrates a graph of flow vs time for a conventional ventilator when the ventilator is in a first mode;

Figure 2 , which is labelled "PRIOR ART", illustrates a graph of nitric oxide concentration vs time corresponding to the graph of Figure 1;

Figure 3, which is labelled "PRIOR ART", illustrates a graph of flow vs time for a conventional ventilator when the ventilator is in a second mode;

Figure 4 , which is labelled "PRIOR ART", illustrates a graph of nitric oxide concentration vs time corresponding to the graph of Figure 3;

Figure 5 schematically illustrates an injection system according to an embodiment of the present invention, the injection system being installed to a conventional ventilator;

Figure 6 schematically illustrates the injection system of Figure 5 when the injection system is not connected to a ventilator;

Figure 7, illustrates a graph of flow vs time for a injection system according to the present invention, the inspiratory phase illustrated could represent a long inspiration;

Figure 8 illustrates a graph of nitric oxide concentration vs time corresponding to the graph of Figure 7;

Figure 9, illustrates a graph of flow vs time for a injection system according to the present invention, the inspiratory phase illustrated could represent a short inspiration;

Figure 10 illustrates a graph of nitric oxide concentration vs time corresponding to the graph of Figure 9;

Figure 11 illustrates a graph of flow vs time for a injection system according to the present invention, the inspiratory phase illustrated generally representing a long inspiration, the flow of injected gaseous substance being modified during the same inspiration;

Figure 12 illustrates a graph of nitric oxide concentration vs time corresponding to the graph of Figure 11;

Figure 13, illustrates a graph of flow vs time for a injection system according to the present invention, the inspiratory phase illustrated generally representing a long inspiration, the flow of injected gaseous substance being modified during the same inspiration;

Figure 14 illustrates a graph of nitric oxide concentration vs time corresponding to the graph of Figure 13;

Figure 15 is a block diagram showing the simplified operation of the injection system of Figure 5;

Figure 16 is a block diagram showing the operation of the injection system of Figure 5, including safety features;

Figure 17 illustrates a graph of flow vs time for a injection system according to the present invention, the inspiratory phases illustrated generally representing long inspirations, the flow of injected gaseous substance being modified between consecutive inspirations;

Figure 18 illustrates a graph of nitric oxide concentration vs time corresponding to the graph of Figure 17;

Figure 19 illustrates a graph of flow vs time for a injection system according to the present invention, the inspiratory phases illustrated generally representing long inspirations, the flow of injected gaseous substance being modified between consecutive inspirations; and

Figure 20 illustrates a graph of nitric oxide concentration vs time corresponding to the graph of Figure 19.

## DESCRIPTION OF THE PREFERRED EMBODIMENT

Figure 5 of the appended drawings illustrates an injection system 100 according to an embodiment of the present invention. The injection system 100 includes a user interface unit 101, a control unit 102, a temperature and humidity measuring unit 103, a valve assembly 104 a backup unit 105 an inspiratory gas flowmeter 106 and a gaseous substance flowmeter 107.

The injection system 100 is illustrated in Figure 5 as being connected to a conventional ventilator 108 through a data cable 110, to a source of a gaseous substance 112 through a conduit 114 and to a patient 116 through an inspiratory conduit 118.

It is to be noted that the following description of the injection system 100 will be given with the particular example of nitric

oxide (NO) injection, but that the system 100 could be used to inject other gaseous substance in the respiratory system of a patient.

The source of gaseous substance (NO) 112 includes a NO container 120, a pressure reducer 122 connected to the container 120 and a precision flowmeter 124 adjusting the maximum flow rate of NO in the injection system 100 and connected to the pressure reducer 122. The conduit 114 pneumatically connects the precision flowmeter 124 to a fluid input 126 of the valve assembly 104 and to a fluid input 127 of a backup valve assembly 129 of the backup unit 105 as will be described hereinafter.

The ventilator 108, when in operation, repetitively supplies a predetermined quantity of inspiratory gas to the respiratory system of the patient 116 through the inspiratory conduit 118 connected to an endotracheal tube 128.

The inspiratory gas supplied to the patient goes through the flowmeter 106, via conduit 130, thereby enabling the flowmeter 106 to measure the inspiratory gas flow supplied to the patient 116. Inspiratory gas flow data is supplied to the control unit 102 via a data cable 132, interconnecting an inspiratory gas flow data output 134 of the flowmeter 106 and an inspiratory gas flow data input 136 of the control unit 102. Of course, the inspiratory gas flow data is either in analog or in digital format, compatible with the control unit 102.

The data cable 132 is illustrated in dashed line in Figure 5 since the data cable 132, along with the flowmeter 106, are not

essential to the operation of the injection system 100 when the injection system 100 is connected to a conventional ventilator 108 provided with a flow data output. Indeed, the ventilator 108 includes an inspiratory gas flow data output 138 electrically connected to an inspiratory gas flow data input 140 of the control unit 102 through the data cable 110. The control unit 102 is therefore supplied with inspiratory gas flow data from either the independent flowmeter 106 or the data flow output 138 of the ventilator 108.

The control unit 102 includes a control output 142 electrically connected to a control input 144 of the valve assembly 104 via a control cable 146. The control unit 102 therefore controls the variable opening of the valve assembly 104. The valve assembly 104 may be a normally closed valve assembly or a normally open valve assembly but is advantageously a normally closed valve assembly for safety reasons. Indeed, it is advantageous that the valve automatically closes upon loss of electrical power.

The valve assembly 104 also includes a fluid output 148 pneumatically connected a fluid input 149 of the gaseous substance flowmeter 107 through a conduit 150. The flowmeter 107 includes a fluid output 151 connected to conduit 118 through a conduit 152 and a "Y" junction 153.

As can be seen from Figure 5, the ventilator 108 also includes an expiratory gas inlet 154 connected to the conduit 118 through a conduit 156 and a "Y" junction 158. The patient's expiration gases is therefore returned to the ventilator 108.

The temperature and humidity measuring unit is provided with conventional means to measure relative humidity and temperature and to supply this data to the control unit 102 via a data cable 111. The measure of both humidity and temperature will enable the control unit 102 to determine the precise flow of the inspiratory gas and subsequently adjust the flow of NO.

The user interface unit 101 is connected to the control unit 102 via a data cable 113 enabling the user interface unit 101 to supply data pertaining to user's inputs to the control unit 102 and enabling the control unit 102 to supply data pertaining to information to be displayed on a display portion (not shown) of the user interface unit 101. For example, the user interface unit 101 includes controls operable by the user to determine the desired concentration of NO to be injected, the type of injection (constant or according to a predetermined pattern) and the variation of the NO concentration over time. These two controls will be further described hereinafter.

The display portion (not shown) of the user interface unit 101 can be used to display the following information:

- the total amount of NO injected to the patient (mole);
- the concentration of inspiratory $NO/NO_2$ (calculated) (ppm);
- the decrease of $FiO_2$ following the NO injection (%);
- the flow of NO (cc/min);
- the quantity of NO remaining in the container 120 (litres);
- the NO flow curve; and

- the ventilation flow curve.

It is believed within the skills of one of ordinary skills in the art to design the control unit 102 as to calculate or to obtain the above-mentioned quantities and concentration from the flowmeters and some initial data, and to format them to be displayed on a conventional display device. Or course, other data, such as, for example, the oxygen concentration supplied by the ventilator, is advantageously supplied to the control unit 102 to enable the determination of the $FiO_2$. It is also to be noted that models predicting the $NO_2$ concentration exist and are believed sufficient for the present purpose.

The valve assembly 104 includes a valve portion 160 including the fluid input 126 and output 148 and a valve actuating portion 162 including the control input 144. The valve actuating portion 162 advantageously transduces an electric signal supplied to the control input 144 to a mechanical opening of the valve portion 160.

As mentioned hereinabove, the injection system 100 includes a backup unit 105 intended to be automatically activated should problems occur with the injection system 100. Indeed, since NO is a drug, the abrupt stopping of the injection of NO could be armful to a patient. The backup unit 105 is thus provided with a backup valve assembly 129 having a valve portion 137 including the fluid input 127 and a fluid output 131 connected to the conduit 118 via a conduit 133 and a "Y" junction 135. The backup valve assembly 129 also includes a valve actuating portion 139 connected to the control unit 102 via a data cable 141 to monitor the status of operation of the control unit 102. The flow of

NO through the valve portion 137, when it is open, is manually adjustable by the user. Therefore, the valve portion 137 automatically supplies a predetermined flow of NO should the injection system 100 fail. It is to be noted that this predetermined flow of NO is generally adjusted so as to be small to prevent injuries to the patient.

In a most simple embodiment, the valve portion 137 is a normally open valve that is configured manually and that is kept closed by a power signal coming from the control unit 102 via the data cable 141 and the valve actuating portion 139. If the control circuit 102 fails so that the power signal is no longer present, for example if the electrical power fails, the valve portion 137 reverts to its normally open state. Of course, other types of detection are possible to determine failure of the other elements of the injection system 100.

A monitoring unit 161 may also be connected to a monitoring aperture 163 via a conduit 165 when monitoring is necessary. It is to be noted that continuous monitoring is not believed required for the injection system of the present invention. However, monitoring at the beginning of the injection of NO is advantageous since the user may verify that the concentration of NO injected, as determined by the monitoring unit 161, is equal to the concentration of NO displayed on the user interface unit 101.

In operation, when the control unit 102 determines, with the inspiratory gas flow data supplied by either the flowmeter 106 or the ventilator 108, that the patient enters an inspiratory phase, it generates a control signal, supplied to the valve assembly 104 via the control cable

146, to cause the opening of the valve assembly 104 that will allow NO to be transferred from the container 120 to the respiratory system of the patient's through the conduits 114, 150, 152,118 and endotracheal tube 128. The opening of the valve assembly 104 is variable and is, in a first mode, a function of the inspiratory gas flow data supplied to the control unit 102. Therefore, the concentration of NO injected to the patient during the inspiratory phase is essentially constant since the opening of the valve assembly 104 is proportional to the inspiratory gas flow detected. As will be described hereinafter with reference to Figures 11-14, the concentration of injected NO could be non linear with respect to time.

Turning now to Figure 15, of the appended drawings, a simplified block diagram 200 of the operation of the injection system will be described. When the system is started (step 202) it is initialized (step 203). A sample of the inspiratory gas flow (IGF) is then taken (step 204), and is converted to a digital value (step 206) before being supplied to a comparator (step 208). The threshold level (REF, step 210 and numeral 26 in Figure 5) is also converted to a digital value (step 212) before being supplied to the comparator of step 208.

The comparator then compares IGF and REF to determine if the inspiratory gas flow is greater than the threshold. If so, the valve assembly 104 is activated (step 214) and the opening of the valve 160 by the valve actuating portion 162 is a function of the inspiratory gas flow level (IGF). If not, the valve 160 is deactivated. Of course, as will be described hereinafter, the opening of the valve 160 may be non linear.

Figure 6 of the appended drawings illustrates the injection system 100 used without a ventilator. The only major difference in the operation of the injection system 100 when used without a ventilator is that the inspiratory gas flow data is supplied to the control unit by the flowmeter 106 since the ventilator 108 is not present.

This is a major advantage to be able to use the injection system 100 without a ventilator since the injection of NO may be continued even though the patient 116 does not require a ventilator. The use of the injection system 100 without a ventilator is possible, without danger to the patient, because of the proportional opening of the valve according to the inspiratory gas flow level. Indeed, even if the patient draws short breaths, the concentration of NO with be essentially constant during the inspiratory phases.

Figure 7 of the appended drawings is a graph schematically illustrating the flow 300 vs time for unassisted respiration by a patient. During the inspiratory phase 302 the inspiratory gas flow rise and falls to form a semi-sinusoidal curve. The patient then expires (see expiratory phase 304). When the injection system 100, as illustrated in Figure 6, is used to inject NO to the patient during the inspiratory phase 302, the flow 306 of NO will begin when the inspiratory gas flow reaches a predetermined threshold 308. The rate of NO injection will then follow the inspiratory gas flow. When the inspiratory gas flow falls below the threshold level 308, the flow of NO is stopped. It is to be noted that the scale is different for the inspiratory gas flow and the flow 306 of NO. Indeed, line 306 illustrating the flow of NO is shown scaled up for illustrative purposes.

As can be seen from Figure 8, that schematically illustrates the NO concentration 310 vs time, the concentration of NO is constant during the patient's inspiratory phase.

Figures 9 and 10 are respectively similar to Figures 7 and 8 but illustrate a patient taking a relatively short inspiration. As can be seen from Figure 10, a resulting NO concentration 310' is essentially equal to the NO concentration 310 of Figure 8. Indeed, with the proportional opening of the valve injecting the NO, changes in the inspiratory gas flow does not modify the injected NO concentration.

As will be readily apparent to one skilled in the art, the inspiratory gas supplied to the patient during the beginning of the inspiratory phase will reach the alveola of the patient, and the inspiratory gas supplied to the patient during the end of the inspiratory phase will stay in the trachea and bronchial tree.

Figures 11 and 12 illustrate the operation of the injection system of Figures 5 or 6 when the opening of the valve assembly 104 is not linear but varies in time to deliver a higher concentration 406 of NO during the beginning of the inspiratory phase 402 and to decrease the concentration of NO (see line 408) after a predetermined and programmable time period 410. Indeed, as described hereinabove, the user interface unit 101 includes controls to determine the shape on the NO concentration during each inspiratory phase.

The NO flow pattern illustrated in Figure 12 could be beneficial to a patient who requires a larger concentration of NO in his alveola than in his bronchial tree.

Similarly, Figures 13 and 14 illustrate the operation of the injection system of Figures 5 or 6 when the opening of the valve assembly 104 is not linear but varies in time to deliver a lower concentration 406' of NO during the beginning of the inspiratory phase 402' and to increase the concentration of NO (see line 408') after a predetermined and programmable time period 410'. Again, as described hereinabove, the user interface unit 101 includes controls to determine the shape on the NO concentration during each inspiratory phase.

The NO flow pattern illustrated in Figure 14 could be beneficial to a patient who requires a larger concentration of NO in his bronchial tree than in his alveola.

One skilled in the art will easily be able to modify the configuration of the control unit 102 to achieve the NO concentrations of Figures 12 or 14, or of any other suitable NO concentration.

Turning now briefly to Figures 17 and 18, the control unit 102 may also be configured, via the user interface unit 101, to progressively decrease the NO concentration injected to the patient over a predetermined number of injection phases or over a predetermined time. The flow of NO (500a-500d in Figure 17) is thus decreased of a minute amount at each inspiratory phase 502a-502e to yield decreasing NO concentrations 504a-504d in Figure 18. Of course, many inspiratory

phases (not shown) are taken by the patient between adjacent inspiratory phases illustrated.

Turning now briefly to Figures 19 and 20, the control unit 102 may also be configured, via the user interface unit 101, to progressively increase the NO concentration injected to the patient over a predetermined number of injection phases or over a predetermined time. The flow of NO (600b-600e in Figure 19) is thus increased of a minute amount at each inspiratory phase 602a-602e to yield decreasing NO concentrations 604b-604e in Figure 20. Of course, many inspiratory phases (not shown) are taken by the patient between adjacent inspiratory phases illustrated.

Figure 16 is a block diagram illustrating an other mode of operation of the injection system 100. It is to be noted that the mode of operation of Figure 16 could be used when the injection system 100 is used in conjunction with a ventilator 108 (see Figure 5). However, this mode of operation is advantageously used when the injection system 100 is used without a ventilator as can be seen in Figure 6.

The mode of operation of Figure 16 is similar to the mode of operation of Figure 15. The extra steps, described hereinafter, are taken to provide safe operation of the injection system 100.

In step 216', a first variable ($T_{inj}$), representing the duration of an injection, is reset and a second variable ($T_{bet\ inj}$), representing the duration between injection, in incremented. The formula f(IGF) representing the opening variations of the valve over time is

determined using the data supplied by the user via the user interface unit 101 and other data of the system such as, for example, temperature and humidity data supplied by the measuring unit 103.

Then, in step 218, the second variable $T_{bet\ inj}$ is compared to a predetermined reference number (Y, steps 220 and 222) to activate an alarm and stop the injection system (step 224) should $T_{bet\ inj}$ be greater than Y. This alarm would indicate that there is a condition preventing the normal injection of NO and that supervision is required.

Similarly, in step 214', $T_{inj}$ is incremented and $T_{bet\ inj}$ is reset. Then, in step 226, the second variable $T_{inj}$ is compared to a predetermined reference number (X, steps 228 and 230) to activate an alarm and stop the injection system (step 232) should $T_{inj}$ be greater than X. This alarm would indicate that a malfunction exists in the injection system and that the valve is continuously open.

Of course, the analog to digital conversion steps 206, 212, 222 and 230 could be omitted if the data is already in a digital format.

As will be apparent to one of ordinary skill in the art, the variable opening of the valve assembly 104 is not essentially proportional to the inspiratory gas flow supplied to the patient. Indeed, the opening could be responsive to the inspiratory gas flow in any other suitable manner.

It is to be noted that the concentration of NO and of $NO_2$ (or of any other gaseous substance injected and their derivative) could be monitored downstream from the "Y" junction 153 by using an appropriate monitoring system 161 for the gaseous substance injected.

It is also to be noted that any adequate flowmeter may be used for the flowmeter 106. However, it has been found advantageous to use a pneumotachometer (PNT) since it is already used in medical application, many models are available through different makers, it is approved by the Food & Drug Administration (FDA), it is sufficiently accurate and is reasonably priced, it is known to users and its performances are well documented since it has been used for years. It is however to be noted that PNT usually do not indicate the mass flow of fluid. As will be apparent to one skilled in the art, the control unit 102 may calculate the mass flow of the inspiratory gas and of the NO since it is supplied with the composition of these gases (via the user interface unit 101) and it is supplied with the temperature and relative humidity of the injection system 100 (via the temperature and humidity measuring unit 103).

As it will be easily understood by one skilled in the art, by installing the PNT inside the injection system 100 it is possible to control the condensation on the PNT to prevent a dramatic decrease in precision.

As will be readily apparent to one skilled in the art, the control unit 102 could include an electronic circuit, a programmable micro

controller and/or a microprocessor, to control the operation of the injection system 100.

Although the present invention has been described hereinabove by way of preferred embodiments thereof, it can be modified, without departing from the spirit and nature of the subject invention as defined in the appended claims.

WHAT IS CLAIMED IS:

1. An injection system for the delivery of a gaseous substance from a container to a patient through a conduit coupled to the patient respiratory system; said injection system comprising:

a control unit controlling said injection system;

a valve assembly in connection with the conduit to selectively allow the delivery of the gaseous substance from the container to the conduit; said valve assembly including a valve and valve actuating means allowing variable opening of said valve; said valve actuating means being coupled to said control unit to be controlled thereby; and

a flowmeter quantitatively measuring inspiratory gas flow in the conduit; said flowmeter being coupled to said control unit to supply inspiratory gas flow data thereto;

wherein said control unit controls said valve assembly so that said variable opening of said valve is responsive to said inspiratory gas flow in the conduit.

2. An injection system as recited in claim 1, wherein said variable opening of said valve is proportionally responsive to said inspiratory gas flow in the conduit.

3. An injection system as recited in claim 1, wherein said variable opening of said valve is such that a predetermined concentration of the gaseous substance with respect to the inspiratory gas is achieved.

4. An injection system as recited in claim 3, wherein said predetermined concentration varies within an inspiratory phase of the patient.

5. An injection system as recited in claim 3, wherein said predetermined concentration varies within a plurality of inspiratory phases of the patient.

6. An injection system as recited in claim 1, wherein said control unit opens said valve in response to said inspiratory gas flow when said inspiratory gas flow exceeds a predetermined threshold level; said injection system therefore delivering the gaseous substance only when the patient is in an inspiratory phase.

7. An injection system as recited in claim 6, wherein said control unit includes an alarm actuated when a duration between two consecutive inspiratory phases exceeds a predetermined duration limit.

8. An injection system as recited in claim 6, wherein said control unit includes an alarm actuated when a duration of an inspiratory phase exceeds a predetermined duration limit.

9. An injection system as recited in claims 7 or 8, wherein said injection system is deactivated when said alarm is actuated.

10. An injection system as recited in claim 1, wherein said controlling unit includes a user interface unit configured to receive inputs from a user and to display data to the user

11. An injection system as recited in claims 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, wherein said gaseous substance includes nitric oxide.

12. An injection system for the delivery of a gaseous substance from a container to a patient through a conduit coupled to the patient respiratory system; the respiratory system of the patient being also coupled to a ventilator forcing inspiratory gas therein; said injection system comprising:

a control unit controlling said injection system; said control unit receiving inspiratory gas flow data from the ventilator; and

a valve assembly in connection with the conduit to selectively allow the delivery of the gaseous substance from the container to the conduit; said valve assembly including a valve and valve actuating means allowing variable opening of said valve; said valve actuating means being coupled to said control unit to be controlled thereby;

wherein said control unit controls said valve assembly so that said variable opening of said valve is responsive to said inspiratory gas flow supplied to the patient.

13. An injection system as recited in claim 12, wherein said variable opening of said valve is proportionally responsive to said inspiratory gas flow forced by the ventilator in the respiratory system of the patient.

14. An injection system as recited in claim 12, wherein said variable opening of said valve is such that a predetermined concentration of the gaseous substance with respect to the inspiratory gas is achieved.

15. An injection system as recited in claim 14, wherein said predetermined concentration varies within an inspiratory phase of the patient.

16. An injection system as recited in claim 14, wherein said predetermined concentration varies within a plurality of inspiratory phases of the patient.

17. An injection system as recited in claim 12, wherein said control unit opens said valve in response to said inspiratory gas flow when said inspiratory gas flow exceeds a predetermined threshold level; said injection system therefore delivering the gaseous substance only when the patient is in an inspiratory phase.

18. An injection system as recited in claim 17, wherein said control unit includes an alarm actuated when a duration between two consecutive inspiratory phases exceeds a predetermined duration limit.

19. An injection system as recited in claim 17, wherein said control unit includes an alarm actuated when a duration of an inspiratory phase exceeds a predetermined duration limit.

20. An injection system as recited in claims 18 or 19, wherein said injection system is deactivated when said alarm is actuated.

21. An injection system as recited in claim 12, wherein said controlling unit includes a user interface unit configured to receive inputs from a user and to display data to the user

22. An injection system as recited in claims 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21, wherein said gaseous substance includes nitric oxide.

AMENDED CLAIMS

[received by the International Bureau on 16 September 1998 (16.09.98); original claims 1-22 replaced by amended claims 1-16 (4 pages)]

1. An injection system for the delivery of a gaseous substance from a container to a patient through a conduit coupled to the patient respiratory system; said injection system comprising:

a control unit controlling said injection system;

a valve assembly in connection with the conduit to selectively allow the delivery of the gaseous substance from the container to the conduit; said valve assembly including a valve and valve actuating means allowing variable opening of said valve; said valve actuating means being coupled to said control unit to be controlled thereby; and

a flowmeter quantitatively measuring inspiratory gas flow in the conduit; said flowmeter being coupled to said control unit to supply inspiratory gas flow data thereto;

wherein a) said control unit controls said valve assembly so that said variable opening of said valve is responsive to said inspiratory gas flow in the conduit so as to achieve a predetermined concentration of the gaseous substance with respect to the inspiratory gas, and b) said predetermined concentration varies within a plurality of inspiratory phases of the patient.

2. An injection system as recited in claim 1, wherein said variable opening of said valve is proportionally responsive to said inspiratory gas flow in the conduit.

3. An injection system as recited in claim 1, wherein said control unit opens said valve in response to said inspiratory gas flow when said inspiratory gas flow exceeds a predetermined threshold level;

said injection system therefore delivering the gaseous substance only when the patient is in an inspiratory phase.

4. An injection system as recited in claim 3, wherein said control unit includes an alarm actuated when a duration between two consecutive inspiratory phases exceeds a predetermined duration limit.

5. An injection system as recited in claim 3, wherein said control unit includes an alarm actuated when a duration of an inspiratory phase exceeds a predetermined duration limit.

6. An injection system as recited in claims 4 or 5, wherein said injection system is deactivated when said alarm is actuated.

7. An injection system as recited in claim 1, wherein said controlling unit includes a user interface unit configured to receive inputs from a user and to display data to the user.

8. An injection system as recited in claims 1, 2, 3, 4, 5, 6 or 7, wherein said gaseous substance includes nitric oxide.

9. An injection system for the delivery of a gaseous substance from a container to a patient through a conduit coupled to the patient respiratory system; the respiratory system of the patient being also coupled to a ventilator forcing inspiratory gas therein; said injection system comprising:

a control unit controlling said injection system; said control unit receiving inspiratory gas flow data from the ventilator; and

a valve assembly in connection with the conduit to selectively allow the delivery of the gaseous substance from the container to the conduit; said valve assembly including a valve and valve actuating means allowing variable opening of said valve; said valve actuating means being coupled to said control unit to be controlled thereby; wherein a) said control unit controls said valve assembly so that said variable opening of said valve is responsive to said inspiratory gas flow supplied to the patient so as to achieve a predetermined concentration of the gaseous substance with respect to the inspiratory gas, and b) said predetermined concentration varies within a plurality of inspiratory phases of the patient.

10. An injection system as recited in claim 9, wherein said variable opening of said valve is proportionally responsive to said inspiratory gas flow forced by the ventilator in the respiratory system of the patient.

11. An injection system as recited in claim 9, wherein said control unit opens said valve in response to said inspiratory gas flow when said inspiratory gas flow exceeds a predetermined threshold level; said injection system therefore delivering the gaseous substance only when the patient is in an inspiratory phase.

12. An injection system as recited in claim 11, wherein said control unit includes an alarm actuated when a duration between two consecutive inspiratory phases exceeds a predetermined duration limit.

13. An injection system as recited in claim 11, wherein said control unit includes an alarm actuated when a duration of an inspiratory phase exceeds a predetermined duration limit.

14. An injection system as recited in claims 12 or 13, wherein said injection system is deactivated when said alarm is actuated.

15. An injection system as recited in claim 9, wherein said controlling unit includes a user interface unit configured to receive inputs from a user and to display data to the user

16. An injection system as recited in claims 9, 10, 11, 12, 13, 14 or 15, wherein said gaseous substance includes nitric oxide.

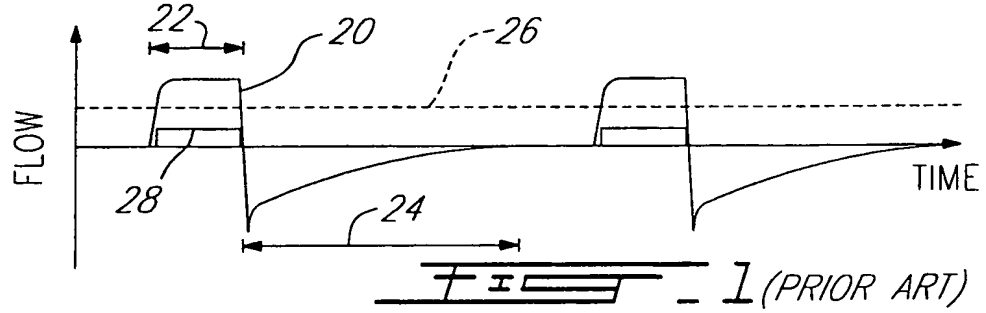


Fig. 1 (PRIOR ART)

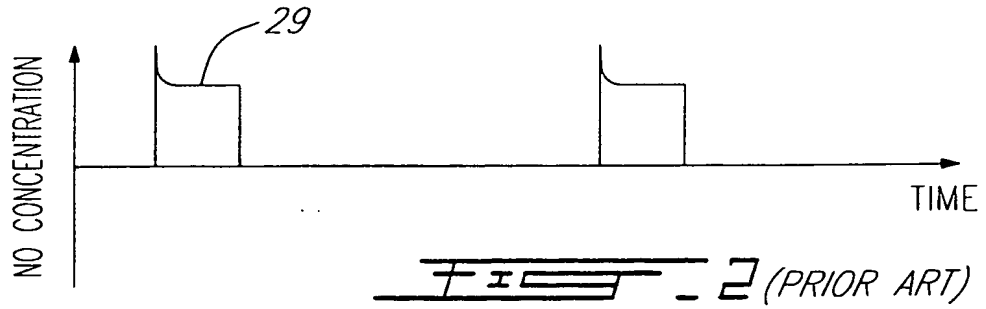


Fig. 2 (PRIOR ART)

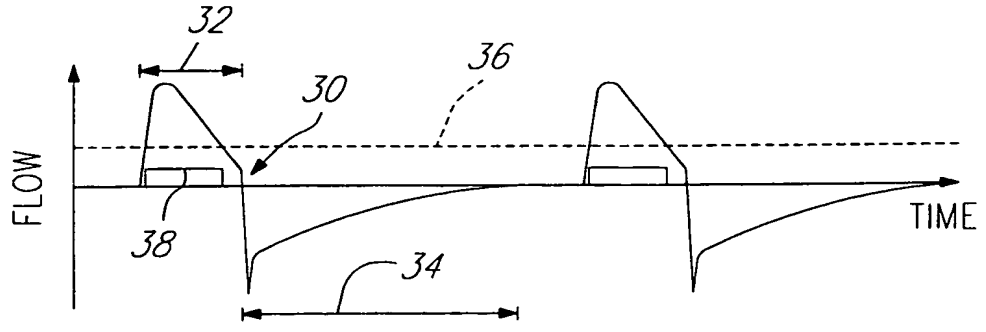


Fig. 3 (PRIOR ART)

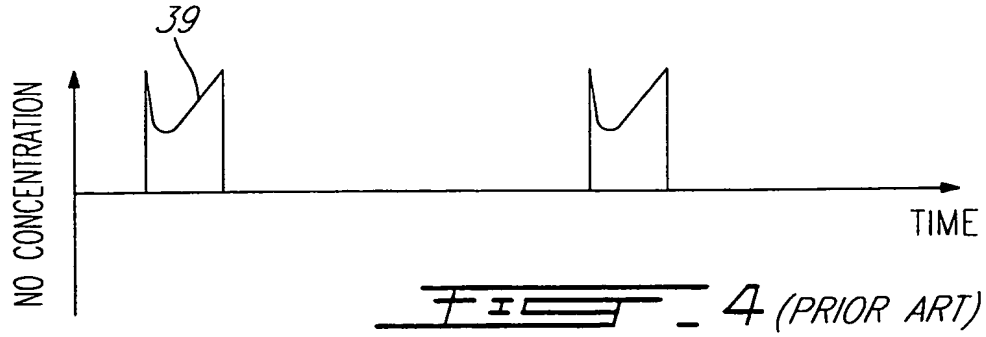


Fig. 4 (PRIOR ART)

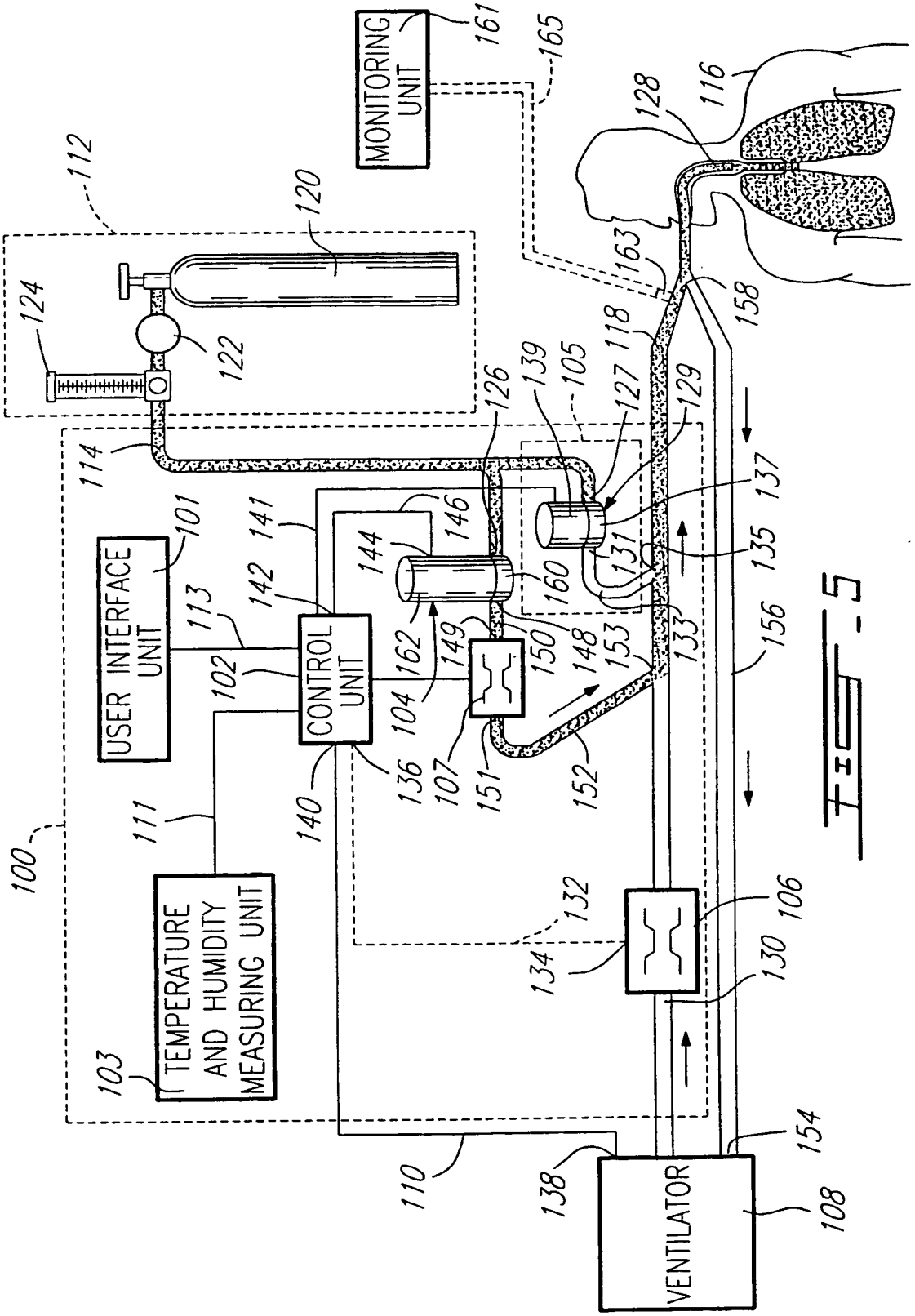
MONITORING UNIT
161
165
112
120
124
122
126
139
105
118
127
129
128
116
163
158
114
137
101
141
146
144
135
131
160
USER INTERFACE UNIT
113
142
102
CONTROL UNIT
162
149
150
148
153
133
156
104
107
151
152
136
140
111
100
TEMPERATURE AND HUMIDITY MEASURING UNIT
103
132
106
134
130
110
138
154
VENTILATOR
108

FIG - 5

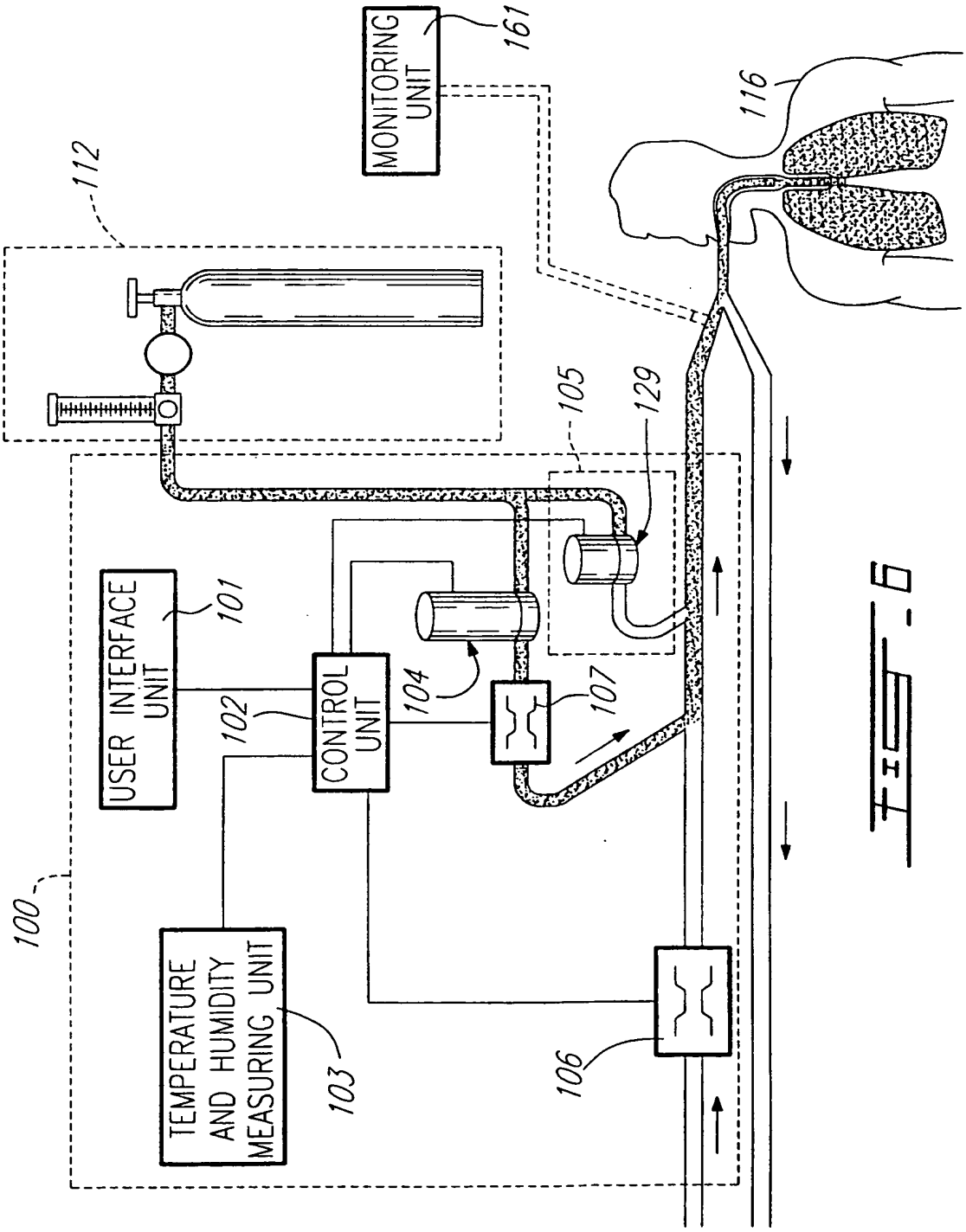
MONITORING UNIT
161
116
112
105
129
USER INTERFACE UNIT
101
102
CONTROL UNIT
104
107
100
TEMPERATURE AND HUMIDITY MEASURING UNIT
103
106

FIG-6

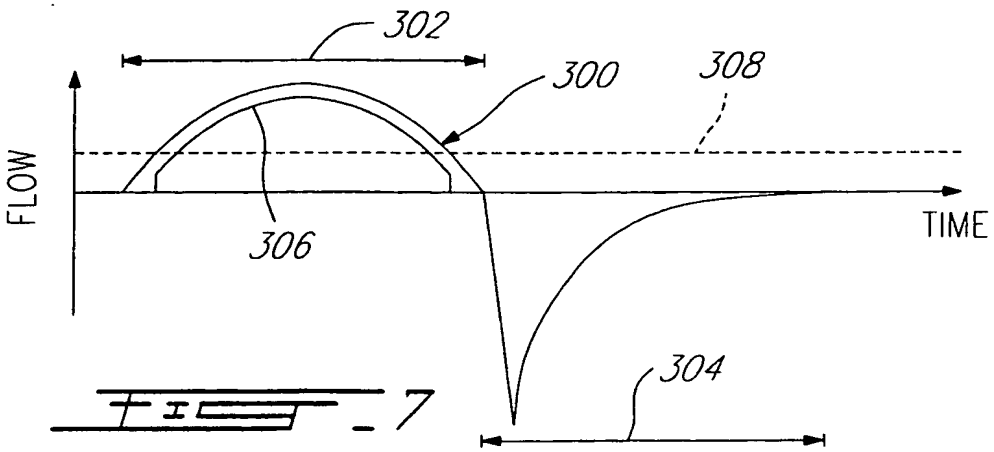


Fig. 7

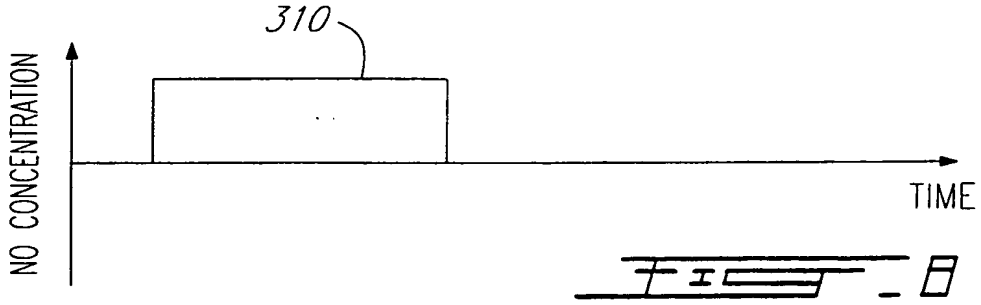


Fig. 8

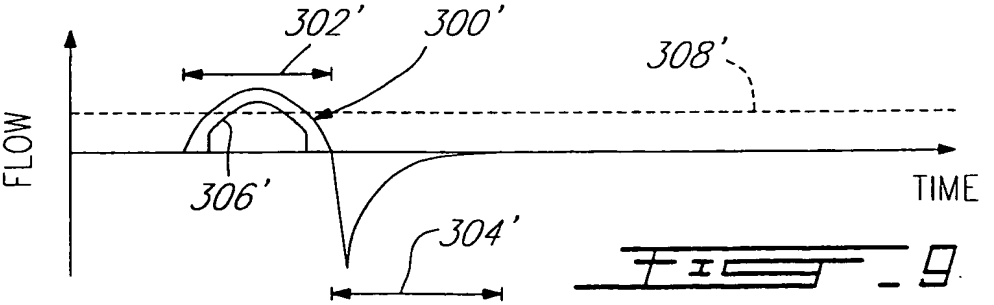


Fig. 9

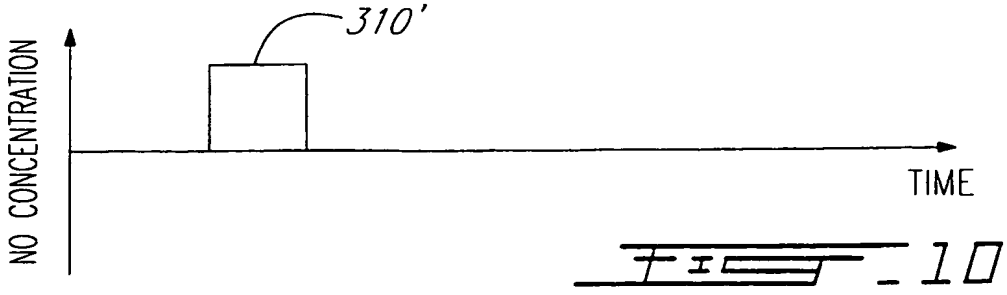


Fig. 10

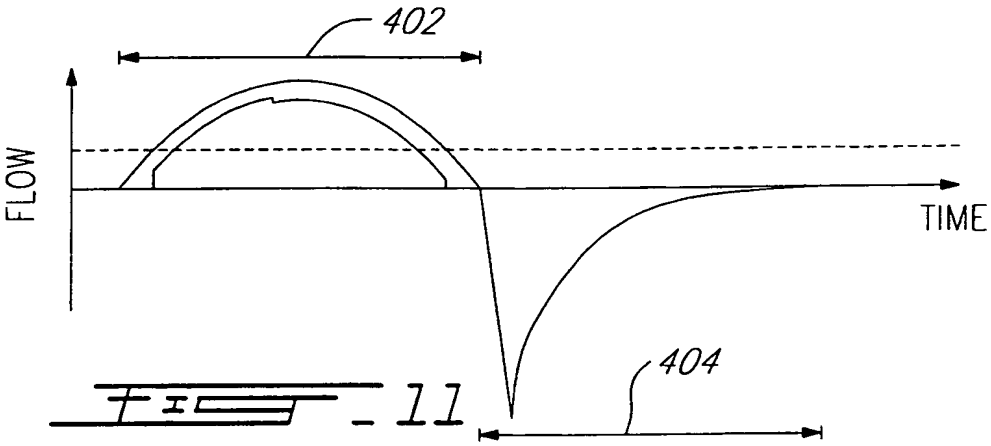


Fig. 11

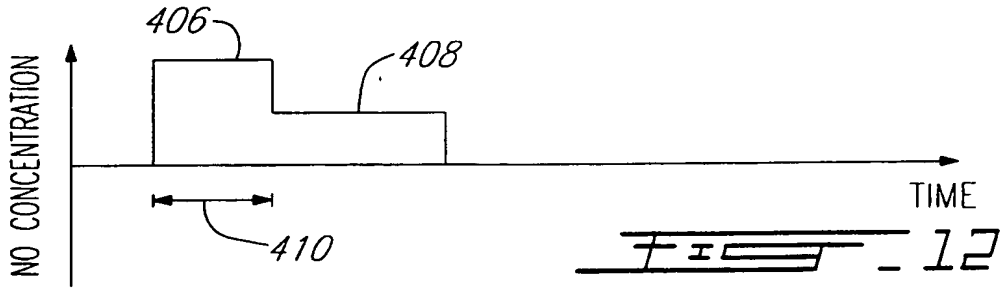


Fig. 12

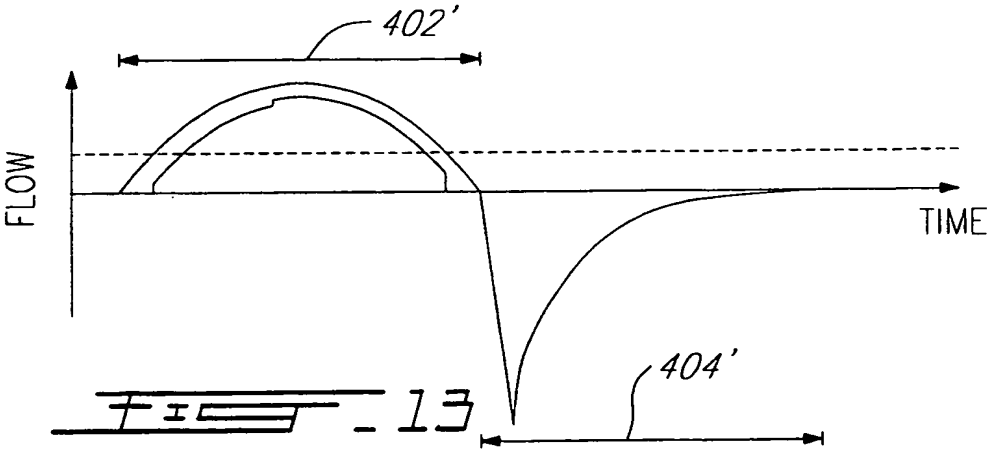


Fig. 13

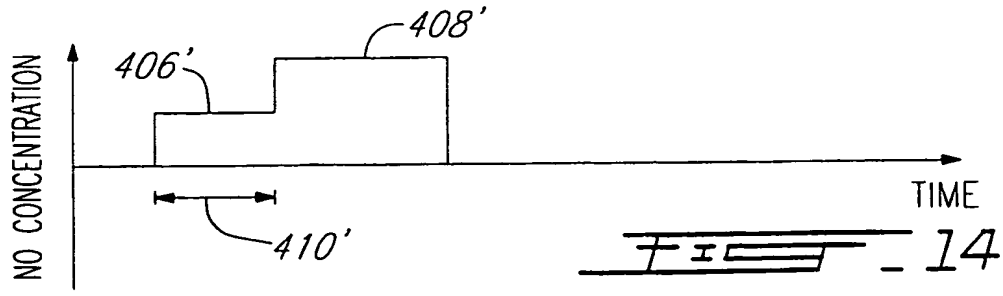


Fig. 14

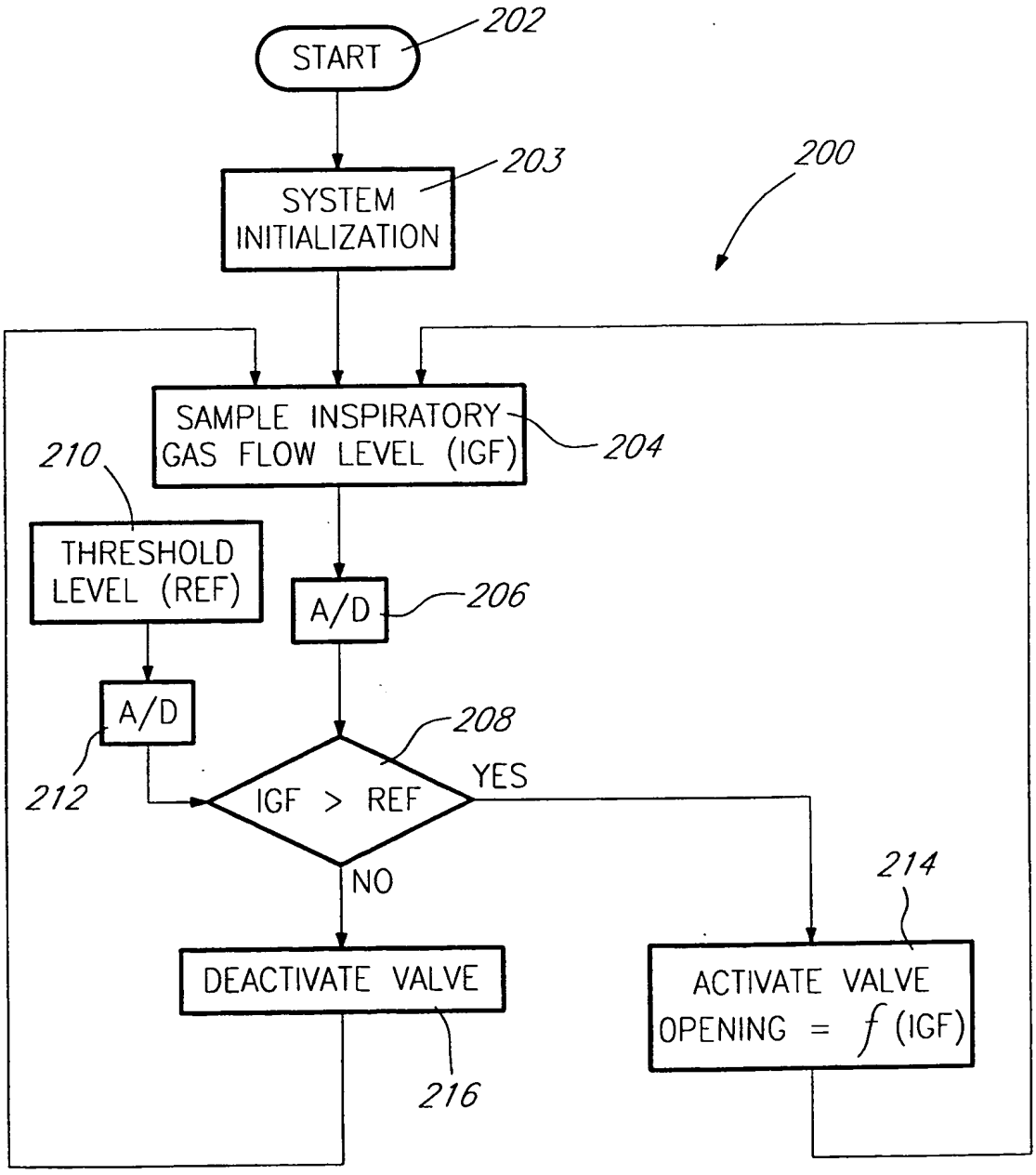
START
202
SYSTEM INITIALIZATION
203
200
SAMPLE INSPIRATORY GAS FLOW LEVEL (IGF)
204
210
THRESHOLD LEVEL (REF)
A/D
206
A/D
212
208
IGF > REF
YES
NO
214
DEACTIVATE VALVE
216
ACTIVATE VALVE OPENING = f (IGF)

Fig. 15

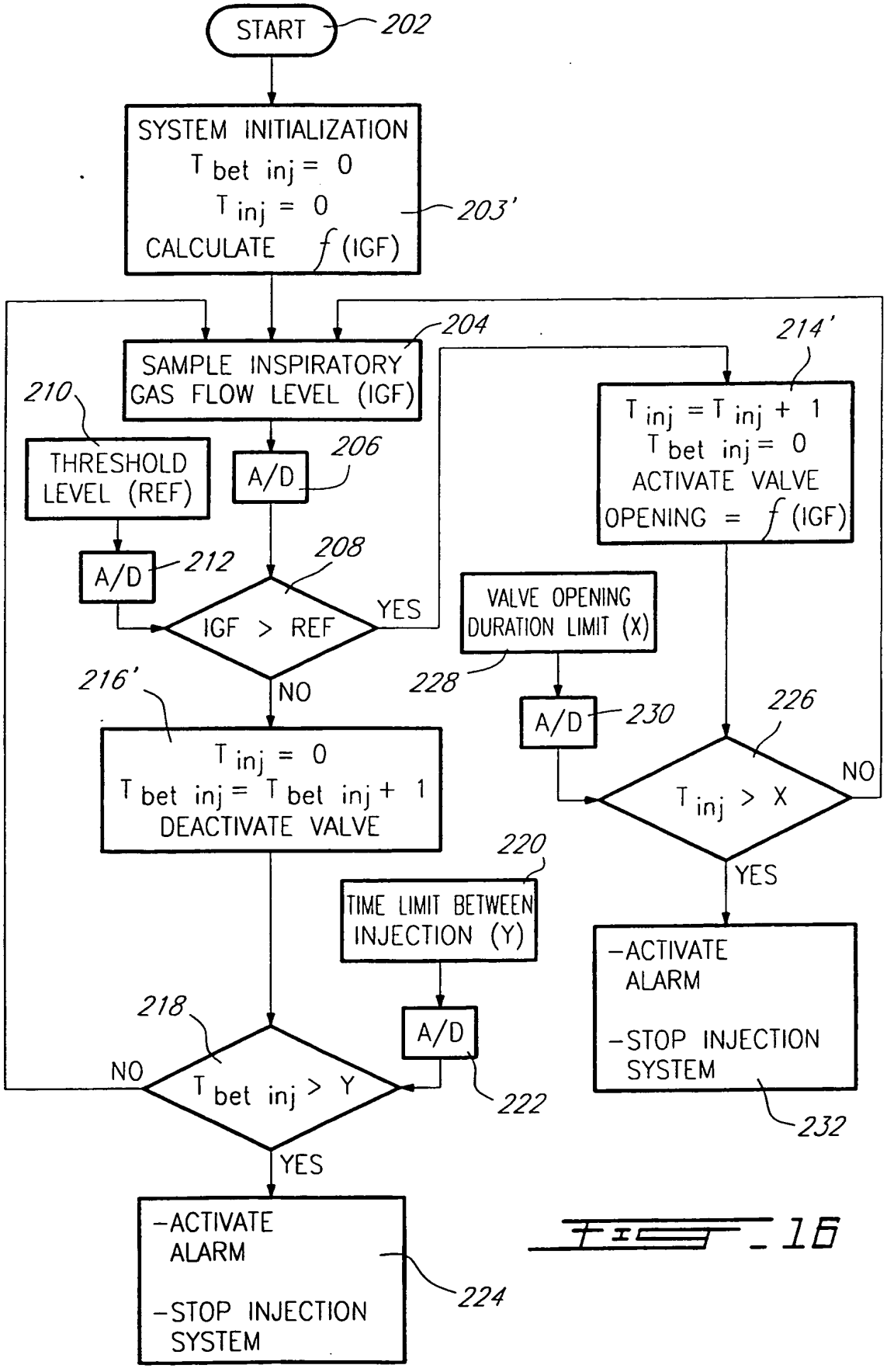
START
202
SYSTEM INITIALIZATION
T bet inj = 0
T inj = 0
CALCULATE f (IGF)
203'
SAMPLE INSPIRATORY GAS FLOW LEVEL (IGF)
204
210
THRESHOLD LEVEL (REF)
A/D
206
A/D
212
208
IGF > REF
YES
NO
216'
T inj = 0
T bet inj = T bet inj + 1
DEACTIVATE VALVE
214'
T inj = T inj + 1
T bet inj = 0
ACTIVATE VALVE
OPENING = f (IGF)
VALVE OPENING DURATION LIMIT (X)
228
A/D
230
226
T inj > X
NO
YES
220
TIME LIMIT BETWEEN INJECTION (Y)
A/D
222
218
T bet inj > Y
NO
YES
-ACTIVATE ALARM
-STOP INJECTION SYSTEM
224
-ACTIVATE ALARM
-STOP INJECTION SYSTEM
232

Fig. 16

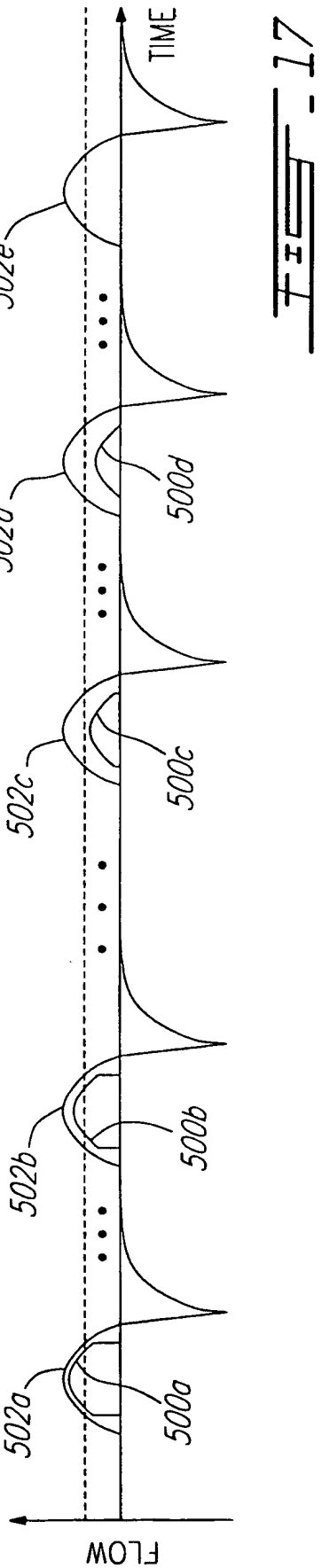
TIME
FLOW
502a
500a
502b
500b
502c
500c
502d
500d
502e

Fig - 17

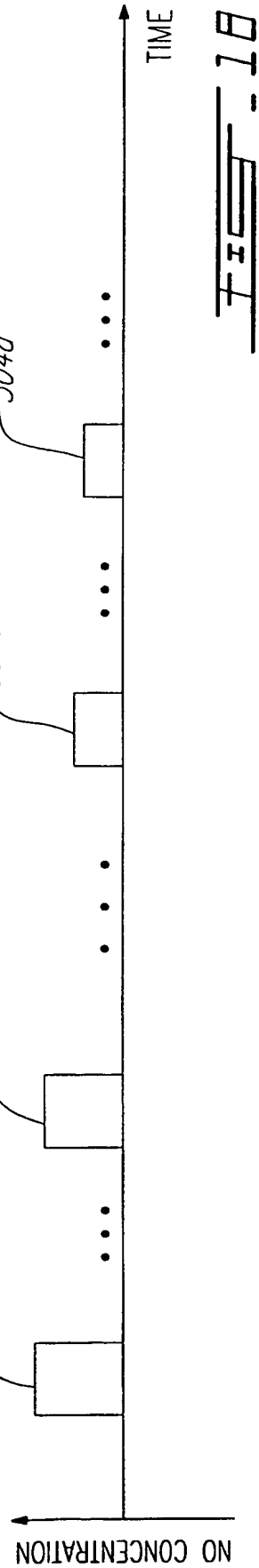
TIME
NO CONCENTRATION
504a
504b
504c
504d

Fig - 18

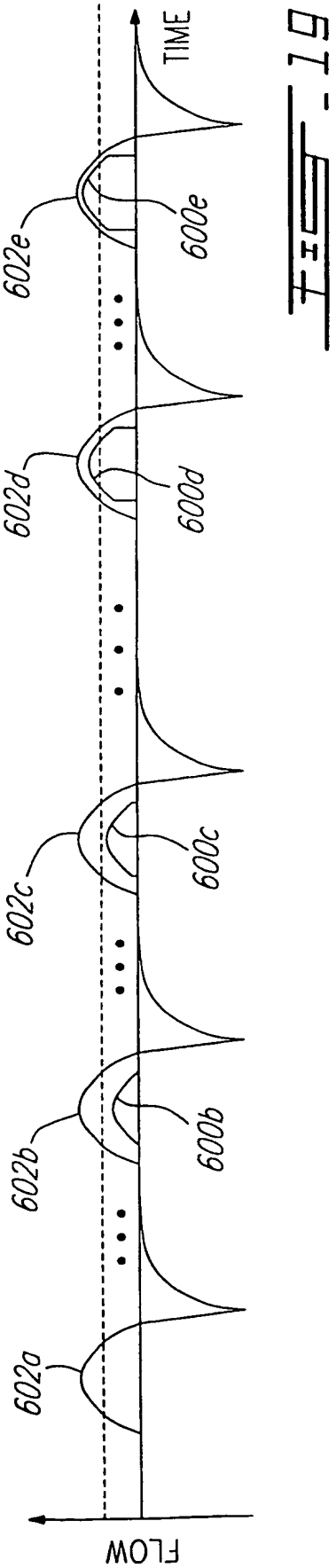
TIME
602e
600e
602d
600d
602c
600c
602b
600b
602a
FLOW

Fig - 19

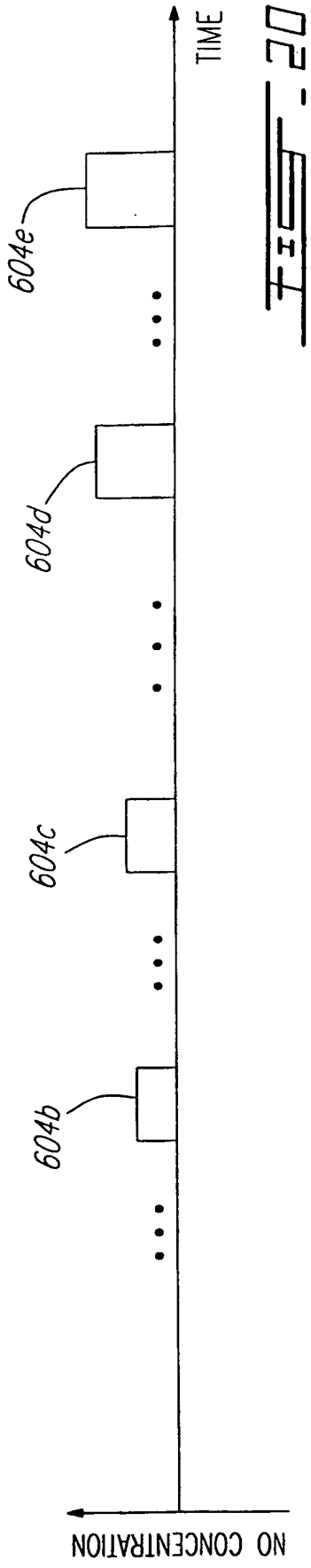
TIME
604e
604d
604c
604b
NO CONCENTRATION

Fig - 20

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 98/00226

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC 6 A61M16/12

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br><br>Y | EP 0 659 445 A (OHMEDA INC) 28 June 1995<br>cited in the application<br><br>see abstract; figure 1<br><br>see column 4, line 5 - line 32<br>see column 6, line 55 - column 7, line 39<br>see column 9, line 8 - line 26<br>see column 10, line 7 - line 17<br>--- | 1-3,<br>10-14,<br>21,22<br>4-9,<br>15-20 |
| Y | WO 95 10173 A (GUSTAFSSON LARS ERIK) 20<br>April 1995<br>see abstract; figures<br>see page 5, line 21 - line 31<br>see page 8, line 15 - line 34<br>see page 10, line 24 - line 29<br>---<br>-/-- | 4,5,15,<br>16 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 29 June 1998 | 17/07/1998 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.<br>Fax: (+31-70) 340-3016 | Zeinstra, H |

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication.where appropnate. of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 96 11717 A (BIRD PRODUCTS CORP) 25 April 1996<br>see abstract; figures 1-3<br>see page 19, line 35 - page 20, line 17<br>see page 30, line 4 - line 30 | 6-9, 17-20 |
| A | US 4 883 050 A (URMAN ROBERT ET AL) 28 November 1989<br>see abstract; figures<br>see column 3, line 4 - line 31 | 7,18 |
| A | LUC DUBÉ ET AL.: "Comparison of two administration techniques of inhaled nitric oxide on nitrogen dioxide production"<br>CAN J ANAESTH,<br>vol. 42, no. 10, 1995,<br>pages 922-927, XP002069682<br>cited in the application<br>see page 924, left-hand column, line 36 - right-hand column, line 4; figures 1-3 | 6,17 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte[redacted]onal Application No
PCT/CA 98/00226

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP 0659445 A | 28-06-1995 | US 5558083 A | 24-09-1996 |
| | | AU 683918 B | 27-11-1997 |
| | | AU 7440794 A | 08-06-1995 |
| | | CA 2133516 A | 23-05-1995 |
| | | JP 2702675 B | 21-01-1998 |
| | | JP 7194705 A | 01-08-1995 |
| | | NZ 264571 A | 22-08-1997 |
| | | ZA 9407680 A | 06-02-1996 |
| WO 9510173 A | 20-04-1995 | AU 7952094 A | 04-05-1995 |
| | | SE 9303369 A | 13-04-1995 |
| WO 9611717 A | 25-04-1996 | EP 0800412 A | 15-10-1997 |
| | | US 5694926 A | 09-12-1997 |
| US 4883050 A | 28-11-1989 | NONE | |

Goudreau Gage Dubuc
& Martineau Walker

PATENT AND TRADEMARK AGENTS

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Internet : mlupien@ggd.com
Your Ref.: PCT/CA98/00226
Our Ref.: ML/12482.8

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Suite 800
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May 20, 1999

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**European Patent Office**
D-80298 Munich
GERMANY

**Attention: Mr. H. Vänttinen**

Subject: International Application No. PCT/CA98/00226
International filing date: April 4, 1997
Applicant: Institut du N.O. Inc.

---

Dear Sir:

This is in response to the PCT Written Opinion mailed on February 25, 1999.

Please amend the above-noted application as follows:

***In the disclosure:***

Please delete pages 6-7 presently on file and substitute therefore amended pages 6-7 enclosed herein.

***In the claims:***

Please delete pages 24-27 and replace therefore with the new amended pages 24-27 including claims 1 to 16 enclosed herein.

***Remarks:***

It is to be noted that the expression "inspiratory phase" used in the claims should be construed as the portion of the *inspiration cycle* where air enters the lungs of the patient. This construction is coherent with both the disclosure and the drawings (see for

example, page 4, line 2, that refers to Figure 3; and page 17, line 18, that refers to Figure 7).

In the above-noted Written Opinion, the Examiner states that the subject matter of claims 1 and 9 does not include an inventive step and gives, in paragraph 1.3, one possible way of overcoming this perceived lack of inventive step. More specifically, the Examiner proposes to clearly indicate that the predetermined concentration can be varied *from one injection phase to another.*

While this is not an indication that the applicant agrees with the Examiner with regards to the lack of inventive step of claims 1 and 9, these claims have been modified according to the suggestion of the Examiner.

It is to be noted that the last paragraph of claims 1 and 9 have been modified to read:

> "... wherein said control unit controls said valve assembly so that a) the variable opening of the valve ..., and b) the predetermined concentration varies from one injection phase to another."

Thereby more clearly stating that the variation of the concentration is controlled by the control unit.

It is also to be noted that pages 6 and 7 of the disclosure have been modified to reflect the amendments of claims 1 and 9.

Yours very truly,

**Goudreau Gage Dubuc**
**& Martineau Walker**

Marc Lupien

ML/fc
Encl.

Goudreau Gage Dubuc
& Martineau Walker

PATENT AND TRADEMARK AGENTS

COPIE

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Our Ref.: MLI12482.8

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September 16, 1998

***BY TELECOPIER***

International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20
Switzerland

Subject: International PCT/CA98/00226
filed on March 13, 1998
Applicant: Institut du N.O. Inc. et al.
Title: INJECTION SYSTEM FOR DELIVERY OF A GASEOUS SUBSTANCE

---

Dear Sirs:

This is in response to the International Search Report mailed on July 17, 1998 in connection with the above-noted application.

In response to this Search Report, please amend the application as follows:

**IN THE DESCRIPTION**:

Please remove pages 5, 6 and 7 and replace with new pages 5, 6 and 7 included herein.

**IN THE CLAIMS**:

Please delete pages 24 to 28 containing claims 1 through 22 and substitute therefore pages 24 to 27 including claims 1 through 16.

**REMARKS**:

New claim 1 includes the subject matter of prior claims 1, 3 and 5. Similarly, new claim 9 contains the subject matter of prior claims 12, 14 and 16.

These independent claims therefore describe an injection system wherein the concentration of the injected gaseous substance may vary over a plurality of inspiratory phases of the patient. This feature is described in the specification from page 19, line 22 to page 20, line 12 and illustrated in Figures 17 through 20.

The documents cited in the above-noted International Search Report do not describe such an injection system allowing the modification of the concentration over a predetermined number of injection phases or over a predetermined time. Indeed, Gustafsson (WO 95 10173 A) describes on page 5, lines 21 to 31, the modification of the concentration during a single inspiratory phase.

It is to be noted that while Gustafsson, on page 10, lines 24 to 29, refers to a predetermined number of inspiration/expiration cycles, he proposes to apply the time variation of this nitric oxide concentration for one inspiration cycle within this predetermined number of cycles. Nothing in this document suggests the modification of the concentration over a plurality of cycles.

The other documents do not describe any modification of concentration over time or over a plurality of inspiratory phases.

It is therefore respectfully submitted that none of the cited documents is particularly relevant to the subject matter of new claims 1 and 9.

Pages 5-7 have been amended to reflect the amendments to the claims.

Respectfully submitted,

**Goudreau Gage Dubuc**
**& Martineau Walker**

Marc Lupien

ML/fc
Encls.

A drawback of the delivery system of Bathe *et al.* is that, while the delivery system may be programmed so that the concentration of NO in the inspiratory gas flow is constant, there are no provisions to modify the concentration of the NO during a particular inspiratory phase, or to program the variation of the concentration of NO over a number of successive inspiratory phases in view of gradually increasing or decreasing the concentration of NO supplied to the patient.

## OBJECTS OF THE INVENTION

An object of the present invention is therefore to provide an improved apparatus for the delivery of gaseous substances.

## SUMMARY OF THE INVENTION

More specifically, in accordance with the present invention, there is provided an injection system for the delivery of a gaseous substance from a container to a patient through a conduit coupled to the patient respiratory system; the injection system comprising:

a control unit controlling the injection system;

a valve assembly in connection with the conduit to selectively allow the delivery of the gaseous substance from the container to the conduit; the valve assembly including a valve and valve actuating means allowing variable opening of the valve; the valve actuating means being coupled to the control unit to be controlled thereby; and

a flowmeter quantitatively measuring inspiratory gas flow in the conduit; the flowmeter being coupled to the control unit to supply inspiratory gas flow data thereto;

wherein a) the control unit controls the valve assembly so that the variable opening of the valve is responsive to the inspiratory gas flow in the conduit so as to achieve a predetermined concentration of the gaseous substance with respect to the inspiratory gas, and b) the predetermined concentration varies within a plurality of inspiratory phases of the patient.

According to another aspect of the present invention, there is provided an injection system for the delivery of a gaseous substance from a container to a patient through a conduit coupled to the patient respiratory system; the respiratory system of the patient being also coupled to a ventilator forcing inspiratory gas therein; the injection system comprising:

a control unit controlling the injection system; the control unit receiving inspiratory gas flow data from the ventilator; and

a valve assembly in connection with the conduit to selectively allow the delivery of the gaseous substance from the container to the conduit; the valve assembly including a valve and valve actuating means allowing variable opening of the valve; the valve actuating means being coupled to the control unit to be controlled thereby;

wherein a) the control unit controls the valve assembly so that the variable opening of the valve is responsive to the inspiratory gas flow supplied to the patient so as to achieve a predetermined concentration of the gaseous substance with respect to the inspiratory gas, and b) the predetermined concentration varies within a plurality of inspiratory phases of the patient.

A major advantage of the present invention concerns the variable opening of the valve to increase or decrease the quantity of the gaseous substance delivered to the patient. Hence, it is possible to control the opening of the valve so that the variable opening of the valve is responsive to the inspiratory gas flow directed towards the respiratory system of the patient and thereby controlling the concentration of the gaseous substance delivered to the patient.

Other objects, advantages and features of the present invention will become more apparent upon reading of the following non restrictive description of preferred embodiments thereof, given by way of example only with reference to the accompanying drawings.

The subject of the present invention was developed at *"Le Département de physique biomédicale, Pavillon Notre-Dame, Centre hospitalier de l'Université de Montréal (CHUM)"*

## BRIEF DESCRIPTION OF THE DRAWINGS

In the appended drawings:

Figure 1, which is labelled "PRIOR ART", illustrates a graph of flow vs time for a conventional ventilator when the ventilator is in a first mode;

Figure 2 , which is labelled "PRIOR ART", illustrates a graph of nitric oxide concentration vs time corresponding to the graph of Figure 1;

WHAT IS CLAIMED IS:

1. An injection system for the delivery of a gaseous substance from a container to a patient through a conduit coupled to the patient respiratory system; said injection system comprising:

a control unit controlling said injection system;

a valve assembly in connection with the conduit to selectively allow the delivery of the gaseous substance from the container to the conduit; said valve assembly including a valve and valve actuating means allowing variable opening of said valve; said valve actuating means being coupled to said control unit to be controlled thereby; and

a flowmeter quantitatively measuring inspiratory gas flow in the conduit; said flowmeter being coupled to said control unit to supply inspiratory gas flow data thereto;

wherein a) said control unit controls said valve assembly so that said variable opening of said valve is responsive to said inspiratory gas flow in the conduit so as to achieve a predetermined concentration of the gaseous substance with respect to the inspiratory gas, and b) said predetermined concentration varies within a plurality of inspiratory phases of the patient.

2. An injection system as recited in claim 1, wherein said variable opening of said valve is proportionally responsive to said inspiratory gas flow in the conduit.

3. An injection system as recited in claim 1, wherein said control unit opens said valve in response to said inspiratory gas flow when said inspiratory gas flow exceeds a predetermined threshold level;

said injection system therefore delivering the gaseous substance only when the patient is in an inspiratory phase.

4. An injection system as recited in claim 3, wherein said control unit includes an alarm actuated when a duration between two consecutive inspiratory phases exceeds a predetermined duration limit.

5. An injection system as recited in claim 3, wherein said control unit includes an alarm actuated when a duration of an inspiratory phase exceeds a predetermined duration limit.

6. An injection system as recited in claims 4 or 5, wherein said injection system is deactivated when said alarm is actuated.

7. An injection system as recited in claim 1, wherein said controlling unit includes a user interface unit configured to receive inputs from a user and to display data to the user.

8. An injection system as recited in claims 1, 2, 3, 4, 5, 6 or 7, wherein said gaseous substance includes nitric oxide.

9. An injection system for the delivery of a gaseous substance from a container to a patient through a conduit coupled to the patient respiratory system; the respiratory system of the patient being also coupled to a ventilator forcing inspiratory gas therein; said injection system comprising:

a control unit controlling said injection system; said control unit receiving inspiratory gas flow data from the ventilator; and

a valve assembly in connection with the conduit to selectively allow the delivery of the gaseous substance from the container to the conduit; said valve assembly including a valve and valve actuating means allowing variable opening of said valve; said valve actuating means being coupled to said control unit to be controlled thereby; wherein a) said control unit controls said valve assembly so that said variable opening of said valve is responsive to said inspiratory gas flow supplied to the patient so as to achieve a predetermined concentration of the gaseous substance with respect to the inspiratory gas, and b) said predetermined concentration varies within a plurality of inspiratory phases ~~of the~~ patient.

10. An injection system as recited in claim 9, wherein said variable opening of said valve is proportionally responsive to said inspiratory gas flow forced by the ventilator in the respiratory system of the patient.

11. An injection system as recited in claim 9, wherein said control unit opens said valve in response to said inspiratory gas flow when said inspiratory gas flow exceeds a predetermined threshold level; said injection system therefore delivering the gaseous substance only when the patient is in an inspiratory phase.

12. An injection system as recited in claim 11, wherein said control unit includes an alarm actuated when a duration between two consecutive inspiratory phases exceeds a predetermined duration limit.

13. An injection system as recited in claim 11, wherein said control unit includes an alarm actuated when a duration of an inspiratory phase exceeds a predetermined duration limit.

14. An injection system as recited in claims 12 or 13, wherein said injection system is deactivated when said alarm is actuated.

15. An injection system as recited in claim 9, wherein said controlling unit includes a user interface unit configured to receive inputs from a user and to display data to the user

16. An injection system as recited in claims 9, 10, 11, 12, 13, 14 or 15, wherein said gaseous substance includes nitric oxide.

a flowmeter quantitatively measuring inspiratory gas flow in the conduit; the flowmeter being coupled to the control unit to supply inspiratory gas flow data thereto;

the control unit controlling the valve assembly so that the variable opening of the valve is responsive to the inspiratory gas flow in the conduit.

According to another aspect of the present invention, there is provided an injection system for the delivery of a gaseous substance from a container to a patient through a conduit coupled to the patient respiratory system; the respiratory system of the patient being also coupled to a ventilator forcing inspiratory gas therein; the injection system comprising:

a control unit controlling the injection system; the control unit receiving inspiratory gas flow data from the ventilator;

a valve assembly in connection with the conduit to selectively allow the delivery of the gaseous substance from the container to the conduit; the valve assembly including a valve and valve actuating means allowing variable opening of the valve; the valve actuating means being coupled to the control unit to be controlled thereby;

the control unit controlling the valve assembly so that the variable opening of the valve is responsive to the inspiratory gas flow supplied to the patient.

A major advantage of the present invention concerns the variable opening of the valve to increase or decrease the quantity of the gaseous substance delivered to the patient. Hence, it is possible to control the opening of the valve so that the variable opening of the valve

is responsive to the inspiratory gas flow directed towards the respiratory system of the patient and thereby controlling the concentration of the gaseous substance delivered to the patient.

Other objects, advantages and features of the present invention will become more apparent upon reading of the following non restrictive description of preferred embodiments thereof, given by way of example only with reference to the accompanying drawings.

The subject of the present invention was developed at *"Le Département de physique biomédicale, Pavillon Notre-Dame, Centre hospitalier de l'Université de Montréal (CHUM)"*

## BRIEF DESCRIPTION OF THE DRAWINGS

In the appended drawings:

Figure 1, which is labelled "PRIOR ART", illustrates a graph of flow vs time for a conventional ventilator when the ventilator is in a first mode;

Figure 2 , which is labelled "PRIOR ART", illustrates a graph of nitric oxide concentration vs time corresponding to the graph of Figure 1;

WHAT IS CLAIMED IS:

1. An injection system for the delivery of a gaseous substance from a container to a patient through a conduit coupled to the patient respiratory system; said injection system comprising:

a control unit controlling said injection system;

a valve assembly in connection with the conduit to selectively allow the delivery of the gaseous substance from the container to the conduit; said valve assembly including a valve and valve actuating means allowing variable opening of said valve; said valve actuating means being coupled to said control unit to be controlled thereby; and

a flowmeter quantitatively measuring inspiratory gas flow in the conduit; said flowmeter being coupled to said control unit to supply inspiratory gas flow data thereto;

wherein said control unit controls said valve assembly so that said variable opening of said valve is responsive to said inspiratory gas flow in the conduit.

2. An injection system as recited in claim 1, wherein said variable opening of said valve is proportionally responsive to said inspiratory gas flow in the conduit.

3. An injection system as recited in claim 1, wherein said variable opening of said valve is such that a predetermined concentration of the gaseous substance with respect to the inspiratory gas is achieved.

4. An injection system as recited in claim 3, wherein said predetermined concentration varies within an inspiratory phase of the patient.

5. An injection system as recited in claim 3, wherein said predetermined concentration varies within a plurality of inspiratory phases of the patient.

6. An injection system as recited in claim 1, wherein said control unit opens said valve in response to said inspiratory gas flow when said inspiratory gas flow exceeds a predetermined threshold level; said injection system therefore delivering the gaseous substance only when the patient is in an inspiratory phase.

7. An injection system as recited in claim 6, wherein said control unit includes an alarm actuated when a duration between two consecutive inspiratory phases exceeds a predetermined duration limit.

8. An injection system as recited in claim 6, wherein said control unit includes an alarm actuated when a duration of an inspiratory phase exceeds a predetermined duration limit.

9. An injection system as recited in claims 7 or 8, wherein said injection system is deactivated when said alarm is actuated.

10. An injection system as recited in claim 1, wherein said controlling unit includes a user interface unit configured to receive inputs from a user and to display data to the user

11. An injection system as recited in claims 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, wherein said gaseous substance includes nitric oxide.

12. An injection system for the delivery of a gaseous substance from a container to a patient through a conduit coupled to the patient respiratory system; the respiratory system of the patient being also coupled to a ventilator forcing inspiratory gas therein; said injection system comprising:

a control unit controlling said injection system; said control unit receiving inspiratory gas flow data from the ventilator; and

a valve assembly in connection with the conduit to selectively allow the delivery of the gaseous substance from the container to the conduit; said valve assembly including a valve and valve actuating means allowing variable opening of said valve; said valve actuating means being coupled to said control unit to be controlled thereby;

wherein said control unit controls said valve assembly so that said variable opening of said valve is responsive to said inspiratory gas flow supplied to the patient.

13. An injection system as recited in claim 12, wherein said variable opening of said valve is proportionally responsive to said inspiratory gas flow forced by the ventilator in the respiratory system of the patient.

14. An injection system as recited in claim 12, wherein said variable opening of said valve is such that a predetermined concentration of the gaseous substance with respect to the inspiratory gas is achieved.

15. An injection system as recited in claim 14, wherein said predetermined concentration varies within an inspiratory phase of the patient.

16. An injection system as recited in claim 14, wherein said predetermined concentration varies within a plurality of inspiratory phases of the patient.

17. An injection system as recited in claim 12, wherein said control unit opens said valve in response to said inspiratory gas flow when said inspiratory gas flow exceeds a predetermined threshold level; said injection system therefore delivering the gaseous substance only when the patient is in an inspiratory phase.

18. An injection system as recited in claim 17, wherein said control unit includes an alarm actuated when a duration between two consecutive inspiratory phases exceeds a predetermined duration limit.

19. An injection system as recited in claim 17, wherein said control unit includes an alarm actuated when a duration of an inspiratory phase exceeds a predetermined duration limit.

20. An injection system as recited in claims 18 or 19, wherein said injection system is deactivated when said alarm is actuated.

21. An injection system as recited in claim 12, wherein said controlling unit includes a user interface unit configured to receive inputs from a user and to display data to the user

22. An injection system as recited in claims 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21, wherein said gaseous substance includes nitric oxide.

PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | **FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
|---|---|---|
| ML/12482.8 | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/CA 98/ 00226 | 13/03/1998 | 04/04/1997 |
| Applicant | | |
| INSTITUT DU N.O. INC. et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [X] the text is approved as submitted by the applicant
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   - [ ] the text is approved as submitted by the applicant
   - [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:
   Figure No. 5
   - [ ] as suggested by the applicant.
   - [X] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

national application No.
PCT/CA 98/00226

**Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)**

A injection system (100) for the delivery of a gaseous substance (1 12) to a patient respiratory system is described herein. The injection system (100) includes a control unit (102) and a valve assembly (104) including a valve (160) and a valve actuator (162) allowing partial opening of the valve (160) and controlled by the control unit (102). The control unit (102) is supplied with gas flow data and controls the valve assembly (104) so that the opening of the valve (160) is a function to the gas flow to thereby enable the control over the concentration of the gaseous substance ( 1 12) delivered to the patient (116).

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 98/00226

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M16/12

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br><br>Y | EP 0 659 445 A (OHMEDA INC) 28 June 1995<br>cited in the application<br><br>see abstract; figure 1<br><br>see column 4, line 5 - line 32<br>see column 6, line 55 - column 7, line 39<br>see column 9, line 8 - line 26<br>see column 10, line 7 - line 17<br>--- | 1-3,<br>10-14,<br>21,22<br>4-9,<br>15-20 |
| Y | WO 95 10173 A (GUSTAFSSON LARS ERIK) 20 April 1995<br>see abstract; figures<br>see page 5, line 21 - line 31<br>see page 8, line 15 - line 34<br>see page 10, line 24 - line 29<br>---<br>-/-- | 4,5,15,<br>16 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 29 June 1998 | 17/07/1998 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Zeinstra, H |

4

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 96 11717 A (BIRD PRODUCTS CORP) 25 April 1996<br>see abstract; figures 1-3<br>see page 19, line 35 - page 20, line 17<br>see page 30, line 4 - line 30 | 6-9, 17-20 |
| A | US 4 883 050 A (URMAN ROBERT ET AL) 28 November 1989<br>see abstract; figures<br>see column 3, line 4 - line 31 | 7,18 |
| A | LUC DUBÉ ET AL.: "Comparison of two administration techniques of inhaled nitric oxide on nitrogen dioxide production"<br>CAN J ANAESTH,<br>vol. 42, no. 10, 1995,<br>pages 922-927, XP002069682<br>cited in the application<br>see page 924, left-hand column, line 36 - right-hand column, line 4; figures 1-3 | 6,17 |

# PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

## PCT

### NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

| | |
|---|---|
| **Date of mailing** (day/month/year)<br>20 November 1998 (20.11.98) | |
| **International application No.**<br>PCT/CA98/00226 | **Applicant's or agent's file reference**<br>ML/12482.8 |
| **International filing date** (day/month/year)<br>13 March 1998 (13.03.98) | **Priority date** (day/month/year)<br>04 April 1997 (04.04.97) |
| **Applicant**<br>BLAISE, Gilbert et al | |

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

02 November 1998 (02.11.98)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

**The International Bureau of WIPO**
**34, chemin des Colombettes**
**1211 Geneva 20, Switzerland**

Facsimile No.: (41-22) 740.14.35

Authorized officer

G. Bornet

Telephone No.: (41-22) 338.83.38

TENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | **FOR FURTHER ACTION** | see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. |
|---|---|---|
| ML/12482.8 | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/CA 98/ 00226 | 13/03/1998 | 04/04/1997 |
| Applicant | | |
| INSTITUT DU N.O. INC. et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
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   - [ ] Transcribed by this Authority

4. With regard to the **title,**
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   - [ ] the text has been established by this Authority to read as follows:

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6. The figure of the **drawings** to be published with the abstract is:
   Figure No. 5
   - [ ] as suggested by the applicant.
   - [X] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.
   - [ ] None of the figures.

# INTERNATIONAL SEARCH REPORT

...on on patent family members

...ational Application No
...T/CA 98/00226

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP 0659445 A | 28-06-1995 | US 5558083 A | 24-09-1996 |
| | | AU 683918 B | 27-11-1997 |
| | | AU 7440794 A | 08-06-1995 |
| | | CA 2133516 A | 23-05-1995 |
| | | JP 2702675 B | 21-01-1998 |
| | | JP 7194705 A | 01-08-1995 |
| | | NZ 264571 A | 22-08-1997 |
| | | ZA 9407680 A | 06-02-1996 |
| WO 9510173 A | 20-04-1995 | AU 7952094 A | 04-05-1995 |
| | | SE 9303369 A | 13-04-1995 |
| WO 9611717 A | 25-04-1996 | EP 0800412 A | 15-10-1997 |
| | | US 5694926 A | 09-12-1997 |
| US 4883050 A | 28-11-1989 | NONE | |

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 96 11717 A (BIRD PRODUCTS CORP) 25 April 1996<br>see abstract; figures 1-3<br>see page 19, line 35 - page 20, line 17<br>see page 30, line 4 - line 30 | 6-9, 17-20 |
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4

# INTERNATIONAL SEARCH REPORT

tional Application No
PCT/CA 98/00226

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M16/12

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br><br>Y | EP 0 659 445 A (OHMEDA INC) 28 June 1995<br>cited in the application<br><br>see abstract; figure 1<br><br>see column 4, line 5 - line 32<br>see column 6, line 55 - column 7, line 39<br>see column 9, line 8 - line 26<br>see column 10, line 7 - line 17<br>--- | 1-3,<br>10-14,<br>21,22<br>4-9,<br>15-20 |
| Y | WO 95 10173 A (GUSTAFSSON LARS ERIK) 20 April 1995<br>see abstract; figures<br>see page 5, line 21 - line 31<br>see page 8, line 15 - line 34<br>see page 10, line 24 - line 29<br>---<br>-/-- | 4,5,15,<br>16 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 29 June 1998 | 17/07/1998 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040. Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Zeinstra, H |

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national application No.
PCT/CA 98/00226

**Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)**

A injection system (100) for the delivery of a gaseous substance (1 12) to a patient respiratory system is described herein. The injection system (100) includes a control unit (102) and a valve assembly (104) including a valve (160) and a valve actuator (162) allowing partial opening of the valve (160) and controlled by the control unit (102). The control unit (102) is supplied with gas flow data and controls the valve assembly (104) so that the opening of the valve (160) is a function to the gas flow to thereby enable the control over the concentration of the gaseous substance ( 1 12) delivered to the patient (116).

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# PATENT COOPERATION TREATY

# PCT

REC'D 30 JUN 1999
WIPO PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| ML/12482.8 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/CA98/00226 | 13/03/1998 | 04/04/1997 |
| International Patent Classification (IPC) or national classification and IPC<br>A61M16/12 | | |
| Applicant<br>INSTITUT DU N.O. INC. et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 02/11/1998 | 28.06.99 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. (+49-89) 2399-0 Tx: 523656 epmu d<br>Fax: (+49-89) 2399-4465 | Authorized officer<br>Vänttinen, H<br>Telephone No. (+49-89) 2399 7442 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA98/00226

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

| | | |
|---|---|---|
| 1-5,8-23 | as originally filed | |
| 6,7 | with telefax of | 25/05/1999 |

**Claims, No.:**

| | | |
|---|---|---|
| 1-16 | with telefax of | 25/05/1999 |

**Drawings, sheets:**

| | |
|---|---|
| 1/9-9/9 | as originally filed |

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**see separate sheet**

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-16 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | 1-16 |
| | No: | Claims | |
| Industrial applicability (IA) | Yes: | Claims | 1-16 |
| | No: | Claims | |

2. Citations and explanations

**see separate sheet**

## VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

**see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

## 1 Concerning Item I

The amended page 5 (see the letter of 16.09.98 sent to International Bureau of WIPO) was not available to the Authorized Officer when this report was established, regardless of the request in the Written Opinion of 25.02.99. Thus, page 5 as filed was considered when establishing this report.

## 2 Concerning Item V

2.1 **State of the Art:** EP-A1-0 659 445 (D1), being considered as the closest prior art, discloses an injection system for the delivery of a gaseous substance, the system comprising a control unit (56), a valve assembly (24) and a flowmeter (46).

The subject-matter of claims 1 and 9 is considered to differ from the disclosure of D1 by that the control unit is adapted to control the valve assembly so that the predetermined concentration varies from one injection phase to another.

**Technical Problem:** Controlling the NO concentration more accurately within an inspiratory phase and from one inspiratory phase to another.

**Solution:** Arranging the control unit to control the valve assembly the variable opening of the valve is responsive to the inspiratory gas flow in the conduit so as to achieve a predetermined concentration of the gaseous substance with respect to respiratory gas and to vary the predetermined concentration from one injection phase to another.

**Argumentation:** The above mentioned solution is new and cannot be derived in an obvious manner from documents cited in the International Search Report and in the description. D1 discloses only that CPU (56) can control the proportional control valve (24) to provide the desired concentration at the next breath based on the measurements made. WO-A-95 10173 discloses in a similar system that the predetermined concentration can be varied within one injection phase, but does not teach the solution of claims 1 and 9. Other documents cited do not either disclose the abovementioned solution. Thus, the subject-matter of claims 1 and 9 is considered to meet the requirements of Articles 33(2) and (3) PCT.

2.2 The dependent **claims 2-8** are concerned with developments of the invention according to claim 1 and **claims 10-16** with developments of the invention according to claim 9, and consequently they appear to fulfil the requirements of Articles 33(2) and (3) PCT as well.

## 3 Concerning Item VII

3.1 The independent **claims 1 and 9** are not in the two-part form in accordance with the Rule 6.3(b) PCT, which in the present case would be appropriate.

3.2 Reference signs in parentheses should be inserted in all the claims to increase their intelligibility, Rule 6.2(b) PCT.

3.3 The "brief description of the drawings" does not include Figure 2 anymore due to the amendment of page 7.

## 4 Concerning Item VIII

**Claims 1 and 9** do not meet the requirements of Article 6 PCT, because they are not clear.

4.1 It is unclear in claim 1 what kind of apparatus features should be defined with the statement "said predetermined concentration varies within plurality of inspiratory phases of the patient". This statement attempts to define the subject-matter in terms of result to be achieved and appears not to allow the skilled person to determine which technical features are required for achieving this result. The above mentioned statement should be formulated in terms of apparatus features allowing the result to be achieved (for example "having means being adapted to...").

It is also unclear if the "inspiratory gas flow in the conduit" (claim 1) is different from "the inspiratory gas flow supplied to the patient" (claim 9). For the assessment of novelty and inventive step they were considered to be the same.

4.2 The vague and imprecise statement "spirit and nature of the subject invention" (page 23, line 6) implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity of the claims when used to interpret them. This statement should therefore be amended to remove this inconsistency.

a flowmeter quantitatively measuring inspiratory gas flow in the conduit; the flowmeter being coupled to the control unit to supply inspiratory gas flow data thereto;

wherein the control unit controls the valve assembly so that a) the variable opening of the valve is responsive to the inspiratory gas flow in the conduit so as to achieve a predetermined concentration of the gaseous substance with respect to the inspiratory gas, and b) the predetermined concentration varies from one injection phase to another.

According to another aspect of the present invention, there is provided an injection system for the delivery of a gaseous substance from a container to a patient through a conduit coupled to the patient respiratory system; the respiratory system of the patient being also coupled to a ventilator forcing inspiratory gas therein; the injection system comprising:

a control unit controlling the injection system; the control unit receiving inspiratory gas flow data from the ventilator; and

a valve assembly in connection with the conduit to selectively allow the delivery of the gaseous substance from the container to the conduit; the valve assembly including a valve and valve actuating means allowing variable opening of the valve; the valve actuating means being coupled to the control unit to be controlled thereby;

wherein the control unit controls the valve assembly so that a) the variable opening of the valve is responsive to the inspiratory gas flow supplied to the patient so as to achieve a predetermined concentration of the gaseous substance with respect to the inspiratory gas, and b) the predetermined concentration varies from one injection phase to another.

AMENDED SHEET

A major advantage of the present invention concerns the variable opening of the valve to increase or decrease the quantity of the gaseous substance delivered to the patient. Hence, it is possible to control the opening of the valve so that the variable opening of the valve is responsive to the inspiratory gas flow directed towards the respiratory system of the patient and thereby controlling the concentration of the gaseous substance delivered to the patient.

Other objects, advantages and features of the present invention will become more apparent upon reading of the following non restrictive description of preferred embodiments thereof, given by way of example only with reference to the accompanying drawings.

The subject of the present invention was developed at *"Le Département de physique biomédicale, Pavillon Notre-Dame, Centre hospitalier de l'Université de Montréal (CHUM)"*

## BRIEF DESCRIPTION OF THE DRAWINGS

In the appended drawings:

Figure 1, which is labelled "PRIOR ART", illustrates a graph of flow vs time for a conventional ventilator when the ventilator is in a first mode;

WHAT IS CLAIMED IS:

1. An injection system for the delivery of a gaseous substance from a container to a patient through a conduit coupled to the patient respiratory system; said injection system comprising:

a control unit controlling said injection system;

a valve assembly in connection with the conduit to selectively allow the delivery of the gaseous substance from the container to the conduit; said valve assembly including a valve and valve actuating means allowing variable opening of said valve; said valve actuating means being coupled to said control unit to be controlled thereby; and

a flowmeter quantitatively measuring inspiratory gas flow in the conduit; said flowmeter being coupled to said control unit to supply inspiratory gas flow data thereto;

wherein said control unit controls said valve assembly so that a) said variable opening of said valve is responsive to said inspiratory gas flow in the conduit so as to achieve a predetermined concentration of the gaseous substance with respect to the inspiratory gas, and b) said predetermined concentration varies from one injection phase to another.

2. An injection system as recited in claim 1, wherein said variable opening of said valve is proportionally responsive to said inspiratory gas flow in the conduit.

3. An injection system as recited in claim 1, wherein said control unit opens said valve in response to said inspiratory gas flow when said inspiratory gas flow exceeds a predetermined threshold level;

AMENDED SHEET

said injection system therefore delivering the gaseous substance only when the patient is in an inspiratory phase.

4. An injection system as recited in claim 3, wherein said control unit includes an alarm actuated when a duration between two consecutive inspiratory phases exceeds a predetermined duration limit.

5. An injection system as recited in claim 3, wherein said control unit includes an alarm actuated when a duration of an inspiratory phase exceeds a predetermined duration limit.

6. An injection system as recited in claims 4 or 5, wherein said injection system is deactivated when said alarm is actuated.

7. An injection system as recited in claim 1, wherein said controlling unit includes a user interface unit configured to receive inputs from a user and to display data to the user.

8. An injection system as recited in claims 1, 2, 3, 4, 5, 6 or 7, wherein said gaseous substance includes nitric oxide.

9. An injection system for the delivery of a gaseous substance from a container to a patient through a conduit coupled to the patient respiratory system; the respiratory system of the patient being also coupled to a ventilator forcing inspiratory gas therein; said injection system comprising:

AMENDED SHEET

a control unit controlling said injection system; said control unit receiving inspiratory gas flow data from the ventilator; and

a valve assembly in connection with the conduit to selectively allow the delivery of the gaseous substance from the container to the conduit; said valve assembly including a valve and valve actuating means allowing variable opening of said valve; said valve actuating means being coupled to said control unit to be controlled thereby;

wherein said control unit controls said valve assembly so that a) said variable opening of said valve is responsive to said inspiratory gas flow supplied to the patient so as to achieve a predetermined concentration of the gaseous substance with respect to the inspiratory gas, and b) said predetermined concentration varies from one injection phase to another.

10. An injection system as recited in claim 9, wherein said variable opening of said valve is proportionally responsive to said inspiratory gas flow forced by the ventilator in the respiratory system of the patient.

11. An injection system as recited in claim 9, wherein said control unit opens said valve in response to said inspiratory gas flow when said inspiratory gas flow exceeds a predetermined threshold level; said injection system therefore delivering the gaseous substance only when the patient is in an inspiratory phase.

12. An injection system as recited in claim 11, wherein said control unit includes an alarm actuated when a duration between two consecutive inspiratory phases exceeds a predetermined duration limit.

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13. An injection system as recited in claim 11, wherein said control unit includes an alarm actuated when a duration of an inspiratory phase exceeds a predetermined duration limit.

14. An injection system as recited in claims 12 or 13, wherein said injection system is deactivated when said alarm is actuated.

15. An injection system as recited in claim 9, wherein said controlling unit includes a user interface unit configured to receive inputs from a user and to display data to the user

16. An injection system as recited in claims 9, 10, 11, 12, 13, 14 or 15, wherein said gaseous substance includes nitric oxide.

AMENDED SHEET